VOLUME 1 • JULY 1959 • NUMBER 1

A.M.A. ARCHIVES OF NEUROLOGY

The A. M. A. Archives of Neurology
Harold G. Wolff

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I. M. Tarlov, A. Giancotti, and A. Rapisarda

Morphology of the Neurosecretory Substances
Leopold Liss

Cerebral Paragonimiasis
S. K. Kim

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Irwin Feigin and Philip Prose

Boston Society of Psychiatry and Neurology

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ITS HISTORY AND TREATMENT

By

BYRON STOOKEY, A.M., M.D.

Professor Emeritus of Clinical Neurological Surgery
College of Physicians and Surgeons, Columbia University
Consultant in Neurological Surgery, Presbyterian Hospital

and

JOSEPH RANSOHOFF, M.D.

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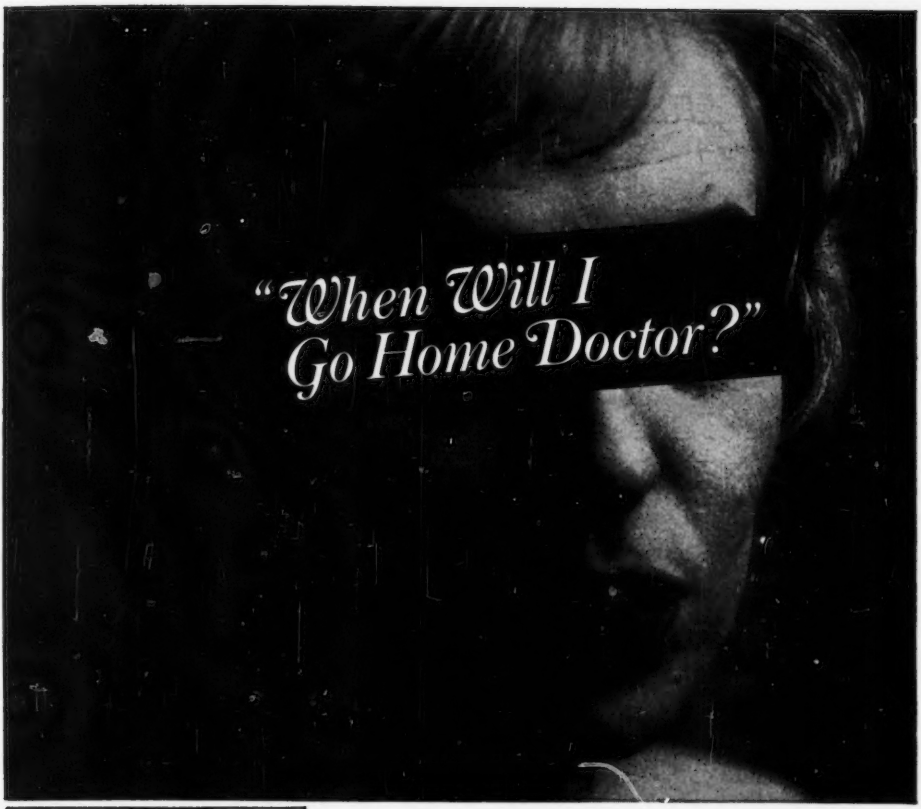

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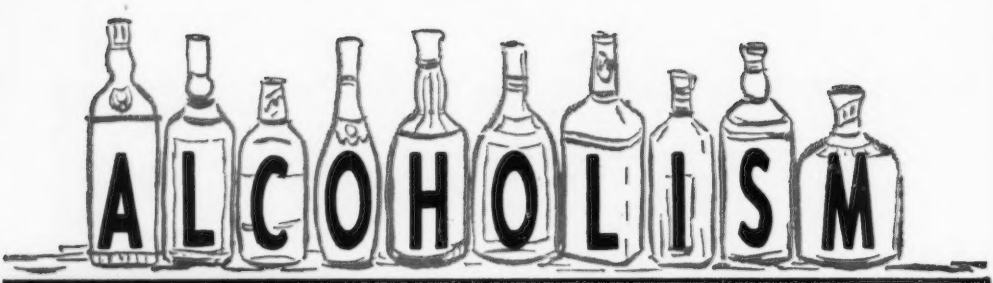

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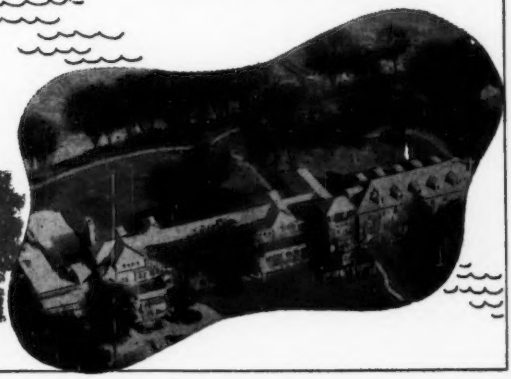

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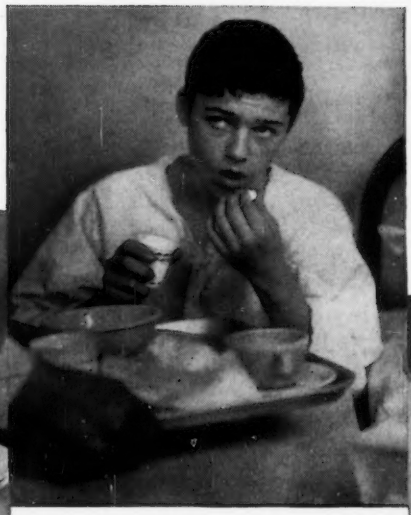

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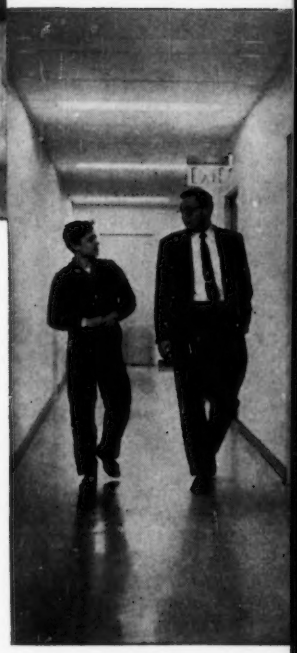
Quiet but alert. Contrite
about smashed window.



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A.M.A. ARCHIVES OF
NEUROLOGY

Editorial

The primary aim of the A. M. A. ARCHIVES OF NEUROLOGY is to further knowledge of clinical neurology, and thus to advance neurological science in general. The earlier triumphs of clinical neurology added greatly to our understanding of motility, sensory and speech disturbances, and the integration of autonomic function. But clinical neurology has now become a broader discipline. As more becomes known about the nervous system, it is evident that these earlier understandings are but the beginnings. Increasing are the indications that a host of metabolic accidents, both inborn and acquired, not only of the brain itself but of other bodily systems as well, are reflected in the malfunction of the cerebrum. The growing awareness of the central regulation of all bodily processes and the telling significance of neurohumoral agents more and more intimately links the neurological sciences with the expanding body of knowledge of the other medical sciences.

The clinical science of Neurology is based upon the oft-repeated observation and study of patients from which stem questions that then require one or another method of investigation for answers. For the most part, these answers are best achieved by the clinician's analysis of phenomena as they exist in the patient. The facts gleaned by the descriptive method, always first in order in the evolution of precise knowledge—the bedrock of medical practice—were derived through the vast and diversified experience of keen minds seeing freshly, schooled but not pedantic. To supplement this, and yielding rich returns, is the experimental method, exemplified by analysis of the experiment of nature, or of that devised by the biologically oriented neurological scientist.

A currently and widely shared notion among physicians is that the study of physics, chemistry, and microbiology has a mystical value and should actually supersede the study of clinical science. But it is the Editor's opinion that clinical science, though it may use many tools, is a discipline, *sui generis*, and that the all-too-hasty flight into the laboratories of chemistry and physics, and into the animal operating rooms of research institutes, to find the answers for bedside problems carries the risk of avoiding, or even of running away from, clinical questions. Whereas meticulous descriptions of clinical phenomena, with more and more about less and less, the malady of the less gifted specialist, end in trivia, the clinician's hope that a better understanding of clinical problems must inevitably follow his personal investigations of the cytological elements of the nervous system, is also often not fulfilled. The analysis of such neuronal elements, per se, should for the most part remain the domain of the basic scientist. Neurologists at the bedside have a unique vantage point and, when they have the eyes to see, are often better able to perceive the fundamental significance to man of the data from the basic sciences than if they were actually working with the intricate tools of the

biophysicist. Clinical scientists, blessed with the opportunity of studying man, often reject this special privilege because they lack belief and confidence in clinical science and in their own ability to devise methods that are humane and give data that are relevant. It is the avowed purpose of the Editors of the ARCHIVES OF NEUROLOGY to bring clinical neurological science into a position of prestige and productiveness.

In short, manuscripts that make genuine contributions to the understanding of clinical phenomena, including diagnosis, etiology, symptoms, signs, and treatment, and of the factors that modify their course are to be given high priority in the ARCHIVES OF NEUROLOGY. Also included in this category are manuscripts that deal with the setting in which disease occurs.

Insofar as manuscripts describing neuropathological material, or chemical, physiological, neurosurgical, electroencephalographic or psychological studies *clearly illuminate neurological clinical states,* they will be given preference. Indeed, today most clinical studies to be effective, require laboratory procedures, often intricate and multiple, be they chemical, physical, or cytological. The editors warmly invite investigators using such methods in the study of patients to turn to the ARCHIVES OF NEUROLOGY for publication of their work. However, studies that deal with technical details, refinements of minor features of procedures, or intradisciplinary controversies had better be referred to special journals devoted to these subjects.

Manuscripts describing experiments performed on laboratory animals will be accorded a second order of acceptance, unless they *especially* illuminate a neurological clinical process, and when the experiments cannot be performed on man. When such laboratory experiments on animals lead to the formulation of *new* and *basic* principles of nervous function, they will be enthusiastically received. Purely comparative anatomical, physiological, pathological, and behavior studies are not suitable for the ARCHIVES OF NEUROLOGY. The widening borderline area opened by neuropharmacology and psychopharmacology should yield facts that press for publication in the ARCHIVES OF NEUROLOGY.

Happily, the acquistion of more printing space will make it possible to shorten the time required for publication of accepted manuscripts. It will also provide opportunities for acceptance of many excellent articles that have had to be rejected in the past, in all fairness to the authors, because of the large backlog of manuscripts that prohibited promise of prompt publication. The manuscripts of the communications read at the annual meetings of the American Neurological Association are submitted to the editors of the ARCHIVES OF NEUROLOGY. Also, abstracts of pertinent reports of papers presented at meetings of the nation's neurological societies will be printed, as well as important announcements of meetings and other significant information. More, and longer, book reviews will be included. The publishing of abstracts of pertinent literature will be continued.

To supplement original articles, the Editor proposes to invite experts to write incisive reviews of clinical interest in which high value will be put upon critical analysis of clinical data. Occasionally, also, a topic in basic science that bears directly upon clinical problems will be presented by an authority in the field. At suitable intervals short editorials will be offered, written by competent experts about new directions and recently opened avenues of investigation and thought.

It is probable that communications will appear in print within four months of the time of acceptance by the Chief Editor.

HAROLD G. WOLFF, M.D.

Acute Intracranial Hypertension

Experimental-Clinical Correlations

I. M. TARLOV, M.D.; A. GIANCOTTI, M.D., and A. RAPISARDA, M.D., New York

It is known that even in expanding lesions that cause fatal rises in intracranial pressure, the Kocher-Cushing guides [6,7,14] for diagnosing severely high intracranial pressure are often absent. These guides are slowing pulse and respirations and steadily rising blood pressure. If the high intracranial tension is not relieved, the pulse begins to rise, blood pressure falls, and respiration stops.

Our purpose was to determine the circumstances under which alterations of these signs may prove helpful in the diagnosis of rapidly expanding brain lesions and in the management of patients suffering from them. We attempted also to clarify the mechanism by which the Kocher-Cushing changes occur.

We used new techniques [21,22] to produce gradually increasing intracranial pressure and to measure pressure within and around the animal brain tissue. To test the results of these experiments, they were correlated with a study of 43 patients suffering from acutely high intracranial pressure. In all cases an autopsy was done.

Experimental Study

A. Method

Dogs were anesthetized with pentobarbital (Nembutal) sodium, injected intravenously (25 mg. per kilogram). Five-millimeter skull holes were drilled in the superior temporal region in one series of dogs and in the suboccipital region in a second series. Through these holes we introduced small latex balloons epidurally so that they lay in the parietotemporal, the frontal, or the occipital region, or else over one cerebellar hemisphere. A balloon so placed was connected by a short metallic tube to a polyethylene tube attached to a bronze bellows driven by a fixed-speed motor (Fig. 1). Compressing the bellows forced Thorotrast (a colloidal suspension of thorium dioxide) into the balloon and gradually expanded it. A fully inflated balloon, with a maximum diameter of 2 cm., usually killed the dog.

Gradual inflation of the balloon compressing the brain of the anesthetized dog could be followed roentgenographically (Fig. 1). Varying with the motor used, the time required for almost full inflation of the balloon was one to eight hours. Inside balloon pressure was measured with a double mercury manometer connected with the compression unit through a T-tube running between the bronze bellows and the balloons.

Mean arterial pressure was measured directly from a cannula inserted in the femoral artery. The cannula, containing sodium citrate solution to prevent blood clotting, led to one arm of a U-shaped mercury manometer. The other arm of the manometer enclosed a float attached to a lever arm and a writing point, which inscribed on a long roll of smoked paper rotating on a double kymograph. The pulse rate was read from the tracing. On the same kymograph the recording lever and writing point of a tambour connected with a pneumograph strapped to the animal's chest traced the rate and amplitude of respirations. We also took note of changes in pupillary size and reactions to light.

In an attempt to obtain precise measurements of intracerebral pressure * we used small latex balloons attached to 18-guage needles introduced into various parts of the cerebral and cerebellar hemispheres. A rigid tube, either needle or catheter, filled with Ringer's solution connected electro-

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* The needle sites were examined at autopsy in all animals. Gross hemorrhage was found but once; in this dog a 1 cm. hemorrhage surrounded the recording needle and balloon placed within the cerebrum.

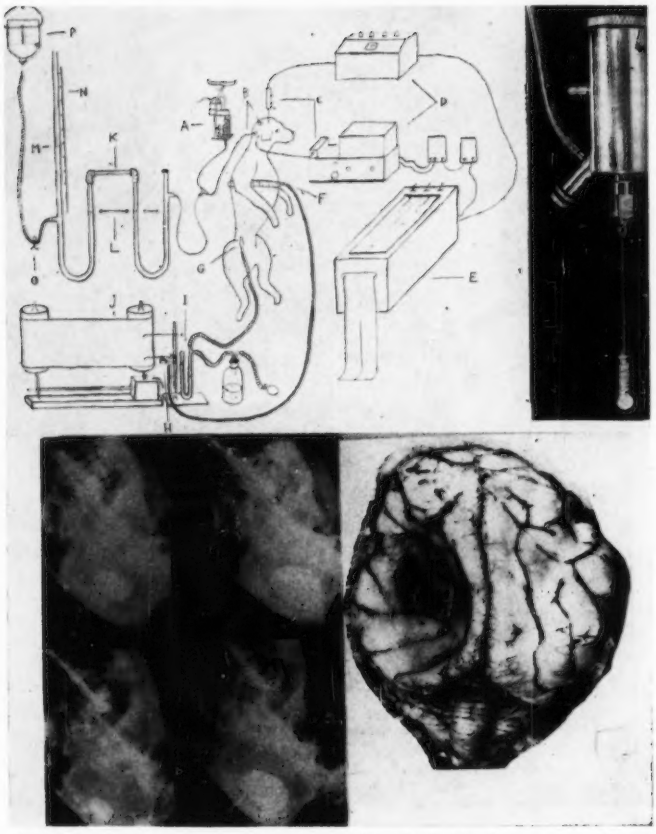

Fig. 1.—Top: drawing showing method of recording dog's blood pressure, pulse, respirations, and infratentorial (intracerebellar) and supratentorial (intracerebral) pressures during gradual inflation of intracranial balloon. *A*, machine for gradual inflation of balloons, *B*, placed in either the supratentorial or the infratentorial space; *C*, transducers actuated by pressure from within cerebral or cerebellar tissue or elsewhere within the intracranial cavity and supplying power through electromanometers, *D*, to activate ink-writing pens for simultaneous recordings of pressure upon paper in *E*. *F*, pneumatic belt connected to pneumatic tambour, *H*, attached to recording lever and writing point inscribing on smoked paper of kymograph, *J*. *G*, cannula within femoral artery connected to mercury manometer, *I*, attached to recording lever and writing point. *K*, double mercury manometer for measuring pressure inside the expanding balloon (*B*) during compression. In order to avoid displacement of fluid from the balloon, the mercury level in the manometer is kept at a constant level, *L*, by varying the height of mercury in the tube, *M*, supplied from the bottle, *P*. *N*, millimeter scale; *O*, clamp.

Photograph on right (top): device, adapted by one of us (A. R.), for measuring pressure within and around the brain. It consists of a latex balloon (3 mm. diameter) attached to an 18-gauge needle connected to the transducer of an electromanometer. Balloon, needle, and transducer are filled with water.

Bottom: series of photographs showing gradual inflation of balloon in supratentorial space. Photograph on right shows compression of brain caused by expanding balloon.

manometers (Sanborn, as well as Lilly types) with water-filled balloons 3 mm. in diameter. Ink-writing pens thus continuously recorded on paper the pressure in the nerve tissue. These balloons were used in five dogs to record pressures alongside the midbrain in the tentorial notch and simultaneously alongside the medulla. They were placed in the subdural space alongside these structures through drill holes in the occipital and suboccipital regions.

With a gradually expanding balloon either in the supratentorial or in the infratentorial space, simultaneous recordings were made of pulse, blood pressure, and respirations, as well as recordings of

pressure in the cerebral and cerebellar hemispheres ipsilateral and contralateral to the expanding balloon and in the balloon itself.

We did 55 experiments, 33 supratentorial and 22 infratentorial. Recordings of intracerebral and intracerebellar pressures were made in 21 animals. The expanding balloon was in the supratentorial space in 12 of these dogs and in the infratentorial space in the other 9. The records of pressures were simultaneous in 10 of these dogs. In one additional dog we made recordings in the right and the left cerebral hemispheres. The pressure rises were the same on the two sides.

After respirations ceased in some dogs and, in others, after the pupils became dilated and fixed to light, we deflated the balloons to study recovery. All dogs were killed so that gross, and in most cases histological, studies of the brain could be made—studies in particular of uncal or cerebellar herniations and brain-stem damage.

B. Results

Supratentorial Compression.—The direct recording of intracerebral pressure during experimental intracranial hypertension has made it possible to study supratentorial and infratentorial pressure variations and their relationship to blood pressure, pulse, and respiratory changes. Three principal stages of supratentorial compression may be distinguished (Fig. 2). During the first stage, compression displaces the cerebrospinal fluid from the cranial cavity and obviously displaces nerve tissue locally. There is no change in intracerebral or intracerebellar pressure at this stage, although pressure alongside the midbrain begins to rise. There is also no change in pulse, respiration, or blood pressure.

During the second stage, brain tissue becomes compressed between the expanding balloon, on one side, and the blood vessels, on the other. This stage manifests changes in vital signs induced by the rise in intracranial pressure, which oscillates with the increased pulsation of the blood pressure. Infratentorial (intracerebellar) pressure rises sooner and higher than supratentorial (intracerebral) pressure. Pressure alongside the midbrain, however, rises sooner and higher than pressure elsewhere within the intracranial cavity. During this second stage the pressure within the brain tissue is for the most part lower than the blood pressure.

During the third stage, pressure in the brain tissue, as well as alongside the midbrain and the medulla, exceeds the lower levels (concave part of the wave) of the

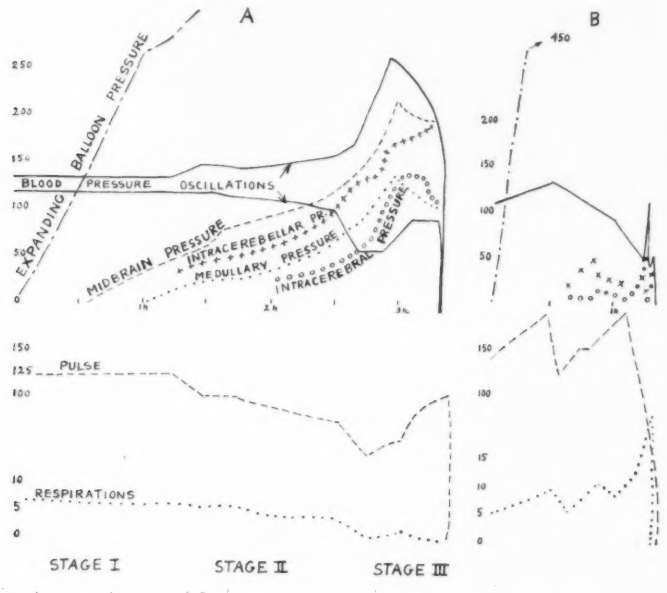

Fig. 2.—Diagrammatic representation of the simultaneous changes in pulse, respirations, blood pressure, expanding balloon pressure, intracerebellar and intracerebral pressure, and pressures alongside midbrain and medulla accompanying gradually increasing intracranial compression in the supratentorial (*A*) and infratentorial (*B*) spaces in a typical experiment.

The figures to the left of the upper diagrams represent pressure, in millimeters of mercury.

The three stages of supratentorial compression do not occur with gradually increasing infratentorial compression.

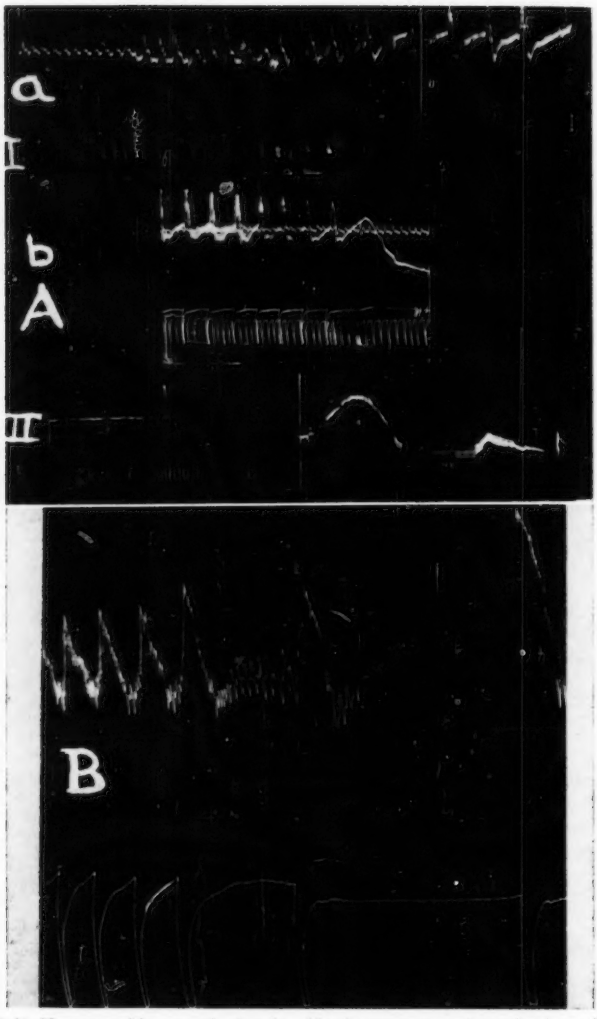

Fig. 3.—(*A*) Kymographic record of pulse, blood pressure, and respirations during a four-hour period of supratentorial compression (*AIa* and *AIb*) and a one-and-one-half-hour period of infratentorial compression (*AII*). Note the rise of blood pressure during the apneic period in (*a*) and its drop during inspiration. The sudden respiratory arrest and the absence of blood-pressure fluctuations accompanying gradually increasing infratentorial compression are seen in *II*.

AIa shows the gradual slowing of respirations and the increased level and amplitude and the rhythmic oscillations of blood pressure.

AIb shows superimposed kymographic tracings of the first and third (last) stages of supratentorial compression. The slowed respirations and the elevated blood pressure are clearly shown. Pulse rate also became slowed (Fig. 4).

AII shows the rather sudden respiratory arrest without preliminary slowing and the drop in blood pressure characteristic of infratentorial compression. The blood-pressure oscillations and gradual increase of level characteristic of supratentorial compression do not occur with infratentorial expanding lesions.

(*B*) kymographic tracing of pulse and blood pressure (above) and respirations (below) during the transition from second to third stage of supratentorial compression. Oscillations of blood pressure gradually increase from amplitudes of 30-40 to 100 mm. of mercury as the respirations slow. The period of apnea shown is one minute, during which the blood pressure steadily rises. Inspiration occurs when the blood pressure reaches its peak; it then falls rather abruptly.

widely oscillating blood pressure (100-250 mm. of mercury); also at this time respirations and, to a less extent, pulse become markedly slower.

Periodic waxing and waning of the arterial pressure (Traube-Hering waves) are synchronous with respiratory movements. But when intracerebral pressure increases and respirations consequently become slower, additional variations in blood pressure occur (Fig. 3). In this instance inspiration is followed by a rapid increase in blood pressure, which falls to its initial level during expiration (Stage II). These are abnormal blood pressure variations, as are those that occur still later, when periods of apnea induce a greater rise in blood pressure (Stage III), especially noticeable terminally. In the terminal stage deep inspiration produces a drop in blood pressure (Fig. 3*B*). Clearly illustrated by this relationship is the close dependence of blood pressure upon respirations, which usually slow down before pulse or blood pressure changes occur and as the intracranial pressure increases.

With a motor designed to inflate fully a balloon in approximately four hours, we found that during the first hour or so, when the inside pressure reaches approximately 250 mm. of mercury, the intracranial pressure does not increase, except slightly alongside the midbrain in the tentorial notch, and there are no alterations of pulse, blood pressure, or respirations. During the next stage (II), while balloon pressure is increasing to 350 mm. of mercury, pressure alongside the midbrain continues to rise, then, after one and one-fourth hours (Fig. 2), the infratentorial (intracerebellar) pressure rises, and finally the supratentorial (intracerebral) pressure rises. At the same time respiratory and pulse rates start slowing, and blood-pressure waves grow larger. Intracerebral pressure varies during this stage (II), increasing somewhat during cardiac systole and decreasing during diastole, and increasing also during expiration and decreasing during inspiration (Fig. 4). Slowing of pulse and respirations becomes more evident. The slowing of respirations (Fig. 4) is accompanied by abnormal blood-pressure waves. A deep inspiration is followed in a few seconds by a rapid increase of blood pressure, which falls slowly to its initial level during expiration.

About 45 minutes later (two and three-fourths hours after beginning of the experiment) pressures have increased still further and reached the hollow of the blood-pressure oscillation waves (100 mm. of mercury), the rise in pressure alongside the midbrain preceding and exceeding the other intracranial-pressure rises. Respirations and pulse continue to slow down (Stage III), and periods of apnea occur, sometimes lasting a minute. At such times blood pressure gradually increases, until a deep inspiration occurs.† It then drops to its preapneic level (Fig. 4). This same cycle may then repeat itself. Finally respirations cease and blood pressure falls. The heart beat often continues for five to six minutes after respirations cease. The rise in intracerebral and intracerebellar pressure accompanying the peak rise in blood-pressure waves is clearly shown in Figure 4. After 3 hours 20 minutes the blood-pressure rise cannot exceed the level of the intracranial pressure. Severe ischemia necessarily results, and the animal dies. Figure 4 illustrates the prior and greater rise in pressure alongside the midbrain than alongside the medulla.

In all cases of supratentorial compression, gradual slowing of respiratory and pulse rates accompanied an increase in amplitude of blood-pressure waves and an increase in blood pressure. In this respect all animals showed the same effects whether the balloons were fully inflated over a one-hour or over an eight-hour period.

In all dogs respirations slowed first, pulse second. Next the homolateral pupil dilated, then the contralateral one. Even when both pupils became dilated and fixed, the dog fully recovered after deflation of the balloon. Respiratory arrest always preceded cardiac arrest. Revival of the dog followed

† Inspiration results in a rise of blood pressure during Stage II of cerebral compression, but in a fall in Stage III.

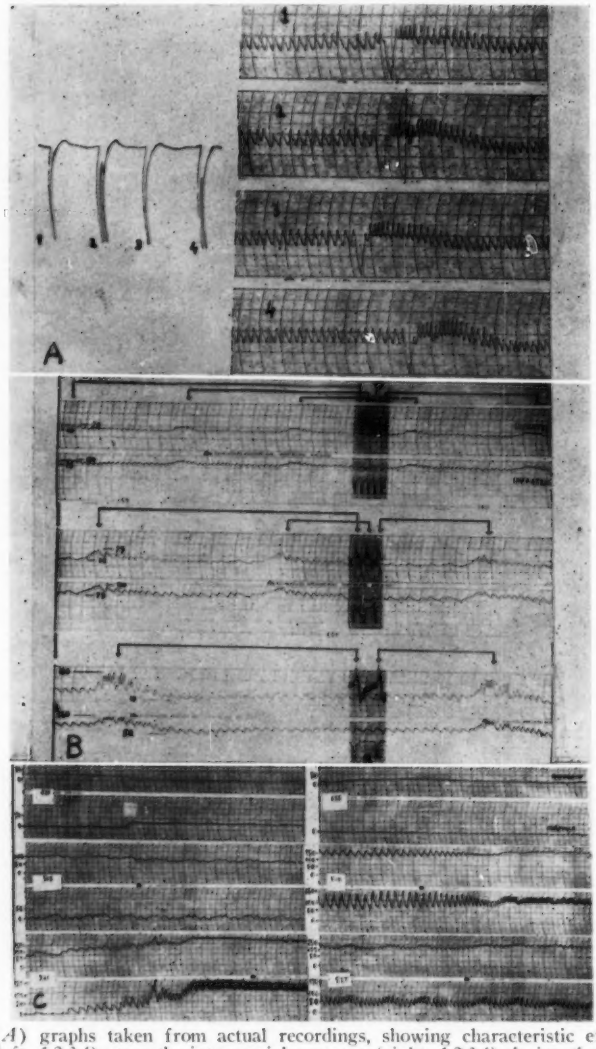

Fig. 4.—(*A*) graphs taken from actual recordings, showing characteristic effect of deep respiration (left, *1,2,3,4*) upon the intracranial pressure (right, *1,2,3,4*) during the second stage of cerebral compression. Note that deep inspiration produces a short-lasting fall of intracranial pressure. The increase of negative intrathoracic pressure accompanying deep inspiration reduces the venous pressure within the brain, thereby lowering intracranial pressure. This effect does not occur during the third stage of intracranial hypertension, probably because the very high venous pressure is inappreciably affected by the lowered thoracic pressure accompanying inspiration.

Note the double lowering of pressure (*2* and *4*)—the second drop being less than the first—accompanying a double inspiration. In *2* the double ellipse running vertically through the center of the paper is an artifact.

(*B*) actual recordings of respirations, blood pressure, and intracerebral and intracerebellar pressures shown in a case of supratentorial compression. The kymographic recording of blood pressure (*P*) and respirations (*R*) are superimposed upon the corresponding tracings of supratentorial (intracerebral) and infratentorial (intracerebellar) pressure. Each tracing has a duration of one and one-half minutes. The three stages of cerebral compression are shown.

Note that in the second stage inspiration is accompanied by a sudden rise in blood pressure and a corresponding rise in intracerebral (supratentorial) and intracerebellar (infratentorial) pressure. During the third stage of cerebral compression the blood pressure increases during apnea, and at the peak of the blood-pressure wave the intracranial pressure reaches its peak. Both then fall as inspiration occurs. The pulse frequency may be observed rising during the blood-pressure increase, and the intracranial pressure rises during the rest of the blood-pressure oscillation. These changes do not occur with infratentorial compression.

(*C*) actual electromanometer recordings, showing subdural-space pressures in the tentorial hiatus alongside the midbrain (upper part of each set of tracings) and alongside the medulla during increasing supratentorial compression. An increase in pressure by the midbrain precedes and exceeds that by the medulla.

deflation of the balloon. After respiratory, but not after cardiac, arrest the dog revived when the balloon was deflated.‡ § ||

In most animals autopsy revealed varying degrees of uncal herniation, usually ipsilateral; and in all animals it revealed midbrain compression, hemorrhage, or venous engorgement, at times all of these changes occurring. Uncal herniation was confined to the side of the compressed hemisphere and was occasionally accompanied by shallow tentorial grooving of the contralateral uncus. Herniation of the ipsilateral cingulate gyrus under the falx cerebri occurred in some of the dogs showing uncal herniations. The tonsillar lobes of the cerebellum herniated through the foramen magnum in two of these dogs.

Midbrain damage may occur without uncal herniation, as was shown by a case of supratentorial compression manifesting the characteristic changes in vital signs but no uncal herniation. Microscopic studies revealed venous strangulation and resultant hemorrhages in the midbrain, which doubtless followed downward transtentorial dislocation of the brain stem.¶

In the 12 of our 15 animals studied histologically, capillary engorgement, perivascular and pericellular edema and hemorrhages, and, in the longer-lasting experiments, chromatolysis of ganglion cells were much more marked in the midbrain than in the medulla. In three animals the histological changes in midbrain and medulla were the same. The cerebrum directly compressed by the expanding balloon was edematous, and at times hemorrhagic. There was no direct continuity between the cerebral and the brain-stem abnormalities.

Subtentorial Compression.—Pressure inside a balloon in the subtentorial space rises much more rapidly than that in a balloon in the supratentorial space (Fig. 2). The pressure inside the balloon attached to the motor that produces fatal compression in about an hour rose to 400 mm. of mercury in about 20 minutes. During this time there was no increase of intracerebral (supratentorial) pressure and only a small increase of intracerebellar (infratentorial) pressure. Meanwhile pulse, respirations, and blood pressure did not change materially.

After 35 minutes of compression intracerebellar and intracerebral pressure rose, the former higher. During this time blood pressure, pulse, and respirations varied slightly, usually rising. After an hour of compression, infratentorial pressure reached the level of blood pressure (60 mm. of mercury), and respirations ceased. In subtentorial compression, unlike supratentorial, blood pressure does not oscillate widely.

‡ In such dogs recovery is heralded by renewed respirations, by lower blood pressure, by smaller fluctuations of blood pressure, and by a resumed normal pulse rate.

§ In one dog nearly dead from rising supratentorial compression, there was an unexpected drop in blood pressure. Renewed respirations and a decrease in the oscillations and level of blood pressure showed that his condition was improving. The mechanism of recovery in such instances is probably as follows: The elevated blood pressure accompanying supratentorial compression increases cardiac thrust. Blood is thus forced into the intracranial cavity, in which the expanding mass causes venous stasis and rise in intracranial pressure. A fall in blood pressure breaks this dangerous circular reaction.

If this explanation is valid, it seems to provide experimental justification for decreasing the elevated blood pressure caused by serious intracranial hypertension in order to gain precious time for palliative or definitive surgical therapy. In some such cases increasing brain tolerance to anoxia through hypothermia would probably also be beneficial. Although clinical data on the efficacy of this practice are difficult to assess, the rationale is sound in cases where intracranial mass does not continue to increase or where the increase is slight.

|| We are now almost continuously recording blood pressure in cases of acute severe intracranial hypertension in the human subject in order to test our animal experiment hypothesis that the course of the blood-pressure oscillations (1) differentiates supratentorial from infratentorial tumefaction and (2) shows whether the intracranial pressure is increasing, decreasing, or remaining stable. For this purpose we use an instrument devised by Kurt Lange.[15] The blood-pressure cuff fits around the patient's arm; the machine is connected to an electric outlet, and the blood pressure is automatically registered on an ink-writing recorder.

¶ The histologic preparations were made by Dr. Rosette Coidan.

During the final stage of apnea blood pressure often rises, then when the dog takes a few breaths, falls. Blood pressure may rise again when breathing stops, then finally fall (Fig. 2).

This same sequence of pressure, pulse, and respiration changes held in all animals, whether the balloon reached full inflation in a half-hour or in four hours.

The progressive slowing of respiratory and pulse rates and the gradual rise and fluctuation of blood-pressure levels accompanying intracerebral hypertension caused by inflation of a supratentorial balloon did not occur when a subtentorial balloon was inflated (Fig. 2).

Only one dog's pupils dilated. The dog's homolateral pupillary dilatation was accompanied by homolateral ptosis and homolateral hemiparesis. Autopsy revealed an upward herniation of the cerebellum through the tentorial notch, as well as a downward herniation of the cerebellar tonsillar lobes through the foramen magnum. Autopsy only occasionally disclosed cerebellar herniation through the foramen magnum.

All eight animals subjected to subtentorial compression and studied histologically showed greater histological changes—capillary engorgement and hemorrhage, perivascular and pericerebellar edema—in the medulla than in the midbrain. The cerebellum directly compressed by the expanding balloon was edematous and at times hemorrhagic.

Figures 2 and 3—simultaneous recordings of the various pressures, of pulse, and of respirations—show the clear-cut differences between dogs subjected to supratentorial and dogs subjected to infratentorial compression.

Comment.—Although we used standard doses of pentobarbital sodium injected intravenously, dogs with infratentorial expanding balloons awoke after one to one and one-half hours of compression, and we had to inject supplementary pentobarbital. On the other hand, reinjections of pentobarbital were never necessary in experiments using expanding supratentorial balloons—even after five to six hours of compression. This experience is compatible with the generally accepted view that pathways concerned with consciousness are concentrated at brain-stem levels cephaled to the medulla.[9]

The increase in intracerebral pressure during expiration and its decrease during inspiration, so clearly shown in our records, are well-known effects of the venous-pressure increase and decrease during expiration and inspiration, respectively. The increase and decrease of intracerebral pressure during cardiac systole and diastole, also shown in our charts, is a purely mechanical effect of the increase and decrease of cardiac thrust.

It is quite evident that our localized supratentorial compression produces the same vital-sign changes as does the generalized intracranial hypertension resulting from the injection of saline solution into the cisterna magna, as reported by Cushing, provided the injection is rapid.# Yet the Kocher-Cushing changes in vital signs do not occur with localized infratentorial compression. Some mechanism in the supratentorial space, it therefore seems, must be responsible for the slowing of pulse and respirations and for the rising blood pressure that accompany acute localized supratentorial compression or very rapidly developing generalized intracranial hypertension.

Normally the respiratory, cardiomotor, and vasomotor centers of the medulla are under control of higher centers in the brain stem and cerebrum. It appears that this higher control is blocked during supratentorial compression and that ischemia, or possibly some other stimulus, then affects the medulla. The experiments of Tsubura,[23] Browder and Meyers,[3] and Forster [8] showed that decerebration did not abolish the respiratory slowing or blood-pressure rise

When we rapidly injected (within 5 to 15 minutes) a large quantity of Ringer's solution (150 cc.) into the cisterna magna, progressive slowing of pulse and respirations and a steady rise of blood pressure followed. These changes did not follow when we injected the fluid slowly (over the course of an hour).

produced by supratentorial compression. Nevertheless, it does not follow that the medullary centers, through their connections with higher brain-stem and cerebral areas, may not produce the changes in pulse, blood pressure, and respirations that accompany acute intracranial hypertension. Hoff and Green [11] and others ** have described pressor responses on stimulation of discrete cerebral and brain-stem areas. It is understandable that stimulating certain pathways, as in the experiments of Hoff and Green, and inhibiting others, as in decerebration, can produce the same results. The loss of certain midbrain influences upon the medulla seems to be the precondition for the Kocher-Cushing changes in vital signs.††

** The change in vital signs occurring during acute supratentorial compression is possibly attributable to a displaced midbrain or to an effect upon discrete parts of the cerebral cortex: the anterior part of the coronal gyrus of the dog, which, when stimulated, slows respirations [4], the cat's or monkey's orbital gyrus, which, when stimulated, slows respiration and increases blood pressure [1]; pathways from the hypothalamus coursing through the brain stem (Ranson and Magoun,[18] which, when stimulated, produce respiratory and cardiac effects (Hess [9]).

†† The following experiment shows that the medulla is an important link in the neuronal chain over which impulses from higher levels slow pulse and respirations and increase blood pressure. After three hours of gradually increasing supratentorial compression in a dog, there were deepening coma, progressively slowing pulse and respirations, and an increase in the level and the oscillations of blood pressure. Pressure alongside the midbrain increased steadily, much more than alongside the medulla. Suddenly cerebellum started oozing from the dural and bony opening through which the pressure-recording balloon had been introduced. Although midbrain pressure kept increasing, blood-pressure level and its oscillations decreased, and pulse and respirations increased to nearly normal. While the dog was still in deep coma, all vital signs suddenly failed. Two repetitions of this experiment gave the same results. The coma accompanying acutely increasing supratentorial compression is doubtless due to midbrain damage. The characteristic cardiorespiratory changes may be due to the same damage. Nevertheless, the medulla is an important pathway for impulses that progressively slow up pulse and respirations and increase blood-pressure level and oscillations.

It is probably not the increased intracranial pressure alone that accounts for the characteristic change in vital signs, but a combination of this pressure with damage to the midbrain from displacement, with or without uncal herniation, and the resultant anoxia. The increased pulsation of the brain, so prominent in cases of supratentorial compression and deriving from the blood-pressure variations, would facilitate displacement. Kahn [13] has observed displacement of the medulla downward after increased supratentorial compression. In his experiments prior displacement of the midbrain probably occurred. Midbrain damage seen in the histological preparations of our animals supports this guess.

Slowed pulse and respirations and elevated blood pressure are characteristic results of supratentorial compression. But since the medulla has important regulatory mechanisms for these effects, why was it that we could not produce the same results with infratentorial compression? Is it possible that these vagal and blood-pressure centers, when compressed by a nearby lesion, respond in an all-or-none manner? In infratentorial compression, to be sure, in contrast to supratentorial compression, between the compressing balloon and brain-stem centers there is no great mass of pulsating nerve tissue, which doubtless promotes transtentorial herniation of the brain stem or the uncus or both. In infratentorial compression the balloon seems to affect directly the medullary centers and cause sudden death.

Clinical Study

We studied 43 patients suffering from acutely increased intracranial pressure (Table). These patients either were admitted to the hospital in coma or became comatose after hospitalization or operation. Studies of pulse, respirations, blood pressure, and status of consciousness were our main concern. The cases are divided into two groups: (1) cases of intracranial hypertension without uncal herniation or midbrain

Cases of Intracranial Hypertension

No. of Cases	Uncal Herniation, or Midbrain Damage, or Both	Changes in Pulse, Respirations, and Blood Pressure
23		
14 neoplasms 9 diffuse brain swelling secondary to diseased other organs	Absent	Pulse and respirations increased; variable blood-pressure changes
10		
7 neoplasms 3 localized hemorrhages	Present	Pulse and respirations slowed; blood pressure usually increased
10		
Neoplasms	Present	Pulse and respirations rapid, with intermittent relative slowing in some cases; variable blood-pressure changes

compression and (II) cases of intracranial hypertension with uncal herniation and midbrain compression.

I. Cases of Intracranial Hypertension Without Uncal Herniation or Midbrain Compression

In 23 of these cases, pulse and respiratory rates were consistently rather high. Blood pressure varied negligibly.

In 9 of the 23 cases there was diffuse brain swelling secondary to disease of other organs; in 4 of the 9, vascular hypertension. Three of the nine cases were due respectively to acute glomerulonephritis, head injury, and obstructive hydrocephalus. In two of the nine cases the etiology of the diffuse brain swelling was undetermined. All nine showed papilledema and generalized convulsions and high pulse and respiratory rates. Usually the blood pressure had fallen, and in no case did it rise steadily. Lumbar puncture, done in five cases, showed an increased pressure. In the fifth of these cases (obstructive hydrocephalus) the pressure was normal.

In three cases in which operation was not done, there was diffuse cerebral swelling, with neoplasms (cerebellar, frontal) and an abscess (cerebellar).

In none of these first 12 cases did autopsy reveal uncal or cerebellar hemorrhage, or evidence of hemorrhage or midbrain compression.

Of 11 additional cases of Group I with postoperative diffuse cerebral swelling, the tumors were supratentorial in 9 and infratentorial in 2. After craniotomy, respirations and pulse increased, but blood pressure remained essentially unchanged (Fig. 5*A*).

After lumbar puncture in 2 of these 11 cases, pulse and respirations suddenly fell to subnormal levels, and the homolateral pupil dilated. In one patient who died within 24 hours after the puncture, there was considerable homolateral uncal edema. Unfortunately, microscopic studies of the midbrain (grossly normal) were not made in these cases.

The pulse and respiratory rates of one of our two patients harboring infratentorial neoplasms showed postoperatively increased pulse and respiratory rates. The second patient ceased breathing at operation and was kept alive for two days with artificial respiration. During this time the pulse rate was high.

II. Cases of Intracranial Hypertension with Uncal Herniation and Midbrain Compression

These 20 cases, all harboring supratentorial expanding lesions, are divided into two subgroups: (*A*) cases with slowing of pulse or respirations or both, and (*B*) cases with no consistent slowing of pulse and respirations.

A. Cases of Uncal Herniation and Midbrain Compression Showing Slowing of Pulse or Respiration or Both.—These 10 cases (7 of neoplasms and 3 of hemorrhage) are the clinical counterpart of the experimental animals with uncal herniations, except that blood-pressure increases were less uniform.

Figure 5*D* shows the changes in vital signs occurring in a 60-year-old hypertensive man who became comatose about two hours after admission to the hospital with the complaint of not feeling well. In spite of his high temperature his pulse and res-

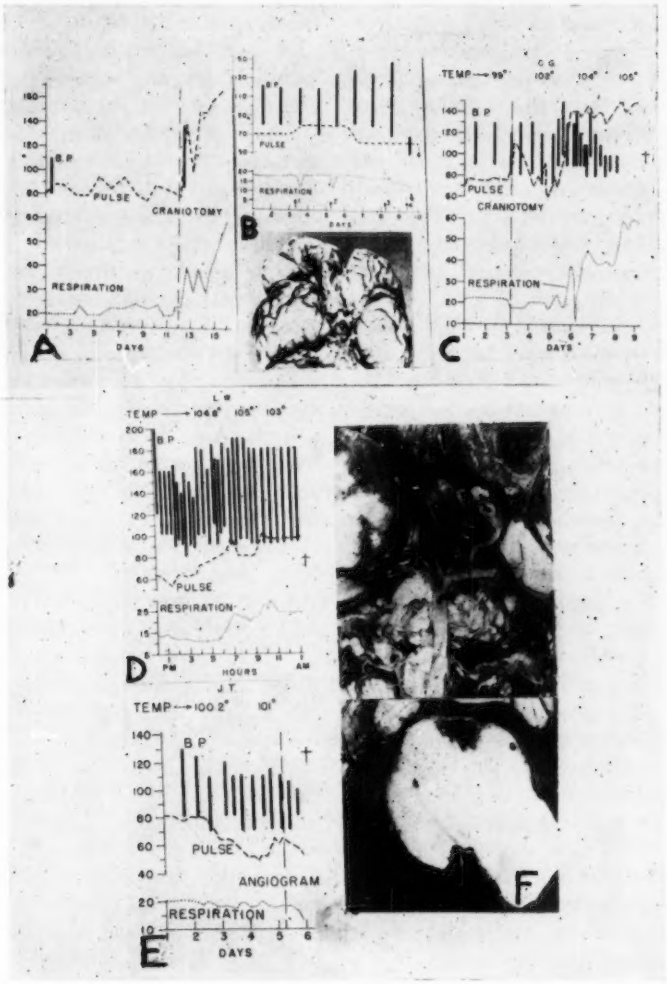

Fig. 5.—(*A*) Patient, aged 65, died after partial removal of bilateral frontal glioblastoma multiforme. Marked brain swelling was observed at autopsy without uncal or cerebellar herniation. Note the elevated postoperative pulse and respiratory rates.

(*B*) Patient, aged 46, succumbed to effects of a right frontoparietal glioblastoma multiforme. Operation was not done. Autopsy disclosed a bilateral uncal herniation, greater on the right side. Note the rather prompt fall in respiratory rates immediately after lumbar puncture done at points *1* and *2*. Convulsions occurred at points *3* and *4*, followed at *3* by generalized rigidity and by bilateral pupillary dilatation at *4*, signs of midbrain compression, found upon sectioning the brain.

(*C*) C. G., aged 55, died after partial removal of a deep right parieto-occipital glioblastoma multiforme. Autopsy disclosed a right uncal herniation and midbrain compression—findings that account for the tendency toward slowing of pulse and respirations during the first few days after operation.

(*D*) L. W., aged 60, succumbed to an intraventricular hemorrhage and a large uncal herniation that compressed the midbrain. Note the slowed respirations and pulse.

(*E*) J. T., aged 25, died after cerebral angiography. Autopsy revealed a large right frontoparietal intracerebral hemorrhage. There was a large right uncal herniation compressing the midbrain, which showed venous engorgement and hemorrhage (*F*).

pirations slowed. His right pupil dilated. Autopsy revealed an intraventricular hemorrhage and a very large uncal herniation, compressing and distorting the midbrain, in which several hemorrhages had occurred.

Figure 5*E* was constructed from the hospital record of a 25-year-old man hospitalized a few hours after he suddenly became hemiplegic on the left and lost consciousness. There then developed a slowing of pulse and respiratory rates, dilatation and fixation of the left pupil to light, and frequent opisthotonic seizures. Coma deepened, and on the fifth day of illness a right cerebral angiography was done, yielding evidence of a ruptured blood vessel in the right frontal lobe. The common carotid artery was therefore ligated in an attempt to lessen the bleeding. The patient became steadily worse and died four hours after the angiography. Autopsy revealed a large right frontoparietal intracerebral hemorrhage and a large uncal herniation compressing the midbrain, which showed venous engorgement and hemorrhages.

Figure 5*B* is a case of uncal herniation on the side of a glioblastoma multiforme. There had been no operation, and pulse and respirations had been slow. The blood pressure had risen moderately until almost the terminal stage, and had then fallen. It is of considerable significance that lumbar puncture and the removal of a few cubic centimeters of cerebrospinal fluid resulted in marked slowing of respirations and a generalized convulsion. On the day before death a lumbar puncture again slowed respirations, and the left pupil became dilated.

B. Cases of Uncal Herniation and Midbrain Compression with Inconsistent Slowing of Pulse or Respirations.—In the 10 patients in this group, all harboring supratentorial neoplasms, autopsy showed uncal herniations and midbrain compression. Before operation either the pulse or the respiratory rate of some of these patients was slow, but after operation, except for one patient, both rates increased. After a left cerebral glioma was removed from one patient whose pulse and respirations had previously been slow, these rates rose relatively slightly. Autopsy disclosed both cerebellar and uncal herniations and compression of both midbrain and medulla.

In one of these patients a steady slowing of pulse (to 40 per minute) and of respirations (to 12 per minute) and a rise in blood pressure followed removal of a large parasagittal frontoparietal meningioma. Coma gradually deepened, and the right pupil became dilated and fixed. It seemed clear that a postoperative blood clot had developed, a supposition confirmed at a second operation. The patient did not regain consciousness, however. After the second operation pulse and respiration rates increased, and autopsy, 10 days later, revealed midbrain hemorrhage but no uncal herniation. In all probability a right uncal herniation had been reduced at the second operation, so that death was doubtless due to the midbrain hemorrhage.

Cases of Groups I and II illustrate the interacting effects of uncal herniations and midbrain compression, on the one hand, and of expanding lesions damaging different cerebral structures regulating vital signs, on the other. The interaction accounts for the deviations from the usual bradycardia and the slow respirations, so often characteristic of midbrain damage. Figure 5*C* is an example of the interaction. This patient had a deep right parieto-occipital glioblastoma multiforme. Craniotomy ordinarily results in increased pulse and respiratory rates. In this case, however (except for periodic slowing of pulse and respirations), for about 72 hours after craniotomy respirations and blood pressure were essentially normal. Then pulse and respiratory rates increased considerably and remained high until death. Autopsy revealed generalized brain swelling, right uncal herniation, and compression of the midbrain.

The Danger of Lumbar Puncture in Intracranial Hypertension

Lumbar puncture may fail to reveal increased intracranial pressure, as the following cases indicate.

One patient (right cerebral glioblastoma multiforme) became drowsy after a lumbar puncture, showing a pressure of only 2 mm. of water. A second patient (right cerebral glioblastoma multiforme) showed a pressure of but 80 mm. of water after lumbar puncture. A third (subdural hematoma and subarachnoid hemorrhage) became comatose after pneumoencephalography showing no increase in pressure. A fourth (right occipital astrocytoma) lost consciousness after a lumbar puncture showing no increase in pressure. Autopsy disclosed marked brain edema and uncal herniations in all these patients.

Lumbar punctures, in our opinion, are much too often used in place of the thought that would show them to be unnecessary.

Comment

Doubtless the most important objective sign of acutely increasing intracranial pressure is blunting of consciousness—drowsiness, stupor, coma. These changes, however, even in combination with neurologic abnormalities, are often insufficient to determine whether the intracranial pressure is rising, or falling, or becoming normal.

The Kocher-Cushing guides to acutely increased intracranial pressure due to expanding brain lesions are inconstant. It has, therefore, been urged that these guides should not be relied on. Our experimental and clinical studies, however, do not support this recommendation. These guides, to be sure, are not always present in acute intracranial hypertension, but, when present, they always indicate a very severe grade of intracranial hypertension due to a supratentorial mass. Close attention to successive recordings of respirations, pulse, and blood pressure and to the state of consciousness, our studies show, often makes it possible to draw reliable inferences concerning intracranial pressure and tell whether the patient is improving, holding his ground, or in need of special medical treatment or operation.

The changes in pulse, respirations, and blood pressure in some patients suffering from severe and rapid cerebral compression are almost identical with our experimental findings in dogs. With or without the rising blood pressure, pulse and respirations become steadily slower only with acutely increased intracranial pressure caused by a rapidly expanding supratentorial mass that promotes a downward herniation of the midbrain or of the temporal lobe (uncus). The herniation, mainly on the ipsilateral side through the tentorial hiatus (tentorial pressure cone)‡‡, subsequently damages the midbrain by compression or by interference with blood supply.§§ In such cases slowing of respirations seems to be the most sensitive and constant indicator of severely increased intracranial pressure; rise in blood pressure, the least constant. In some cases, however, we have observed bradycardia without slow respirations.

Probably midbrain damage—either from primary change (hemorrhage or cell destruction) or from lesions secondary to venous stasis due to transtentorial herniation of the brain stem with or without uncal herniation [19]—may slow either respiration or pulse or both with or without blood pressure changes. Two of our clinical cases, in which such changes in vital signs occurred without uncal herniation, point in this direction. Concomitant injury to neural pathways concerned in slowing down respiration and pulse and in rising blood pressure may possibly account for the absence of these changes in vital signs in certain cases of acutely expanding supratentorial masses accompanied by uncal herniation and midbrain damage.

The hypothalamus, accumulated evidence [9] shows, contains the head nuclei for respiratory and cardiac control, as well as centers concerned with sleep and the degree of consciousness. When there is uncal or

‡‡ It remains to be determined whether, in human cases of rapidly expanding subtentorial masses, upward cerebellar herniation through the tentorium may slow pulse and respirations and raise blood pressure.

§§ In 1920 Adolph Meyer [16] first recognized the importance of subtentorial herniation of the uncus in space-occupying lesions.

transtentorial herniation of the brain stem, compression or ischemia of the hypothalamic pathways may therefore account for slowing pulse and respirations and impaired consciousness. In such cases, decompressing the midbrain by sectioning the tentorium and the incisura tentorii,[12] or otherwise reducing the herniation, may be lifesaving.

In one of our patients the signs of severe midbrain compression caused by uncal herniation were relieved by removing a glioma and a great deal of surrounding softened brain from the temporal and parietal lobes. Tentorial section was unnecessary. A woman from whom a large left frontoparietal parasagittal meningioma had been removed developed the same grave signs but fully recovered after sacrifice of the bone flap. After ventriculography a third patient, with an infiltrating left frontoparietal tumor, showed deepening coma, slowing respirations (2 per minute), increasing blood pressure, and a left pupil fixed and dilated. A large left subtemporal decompression resulted in recovery. These three patients recovered from coma before pulse, respirations, blood pressure, and pupils returned to normal.

When acute intracranial hypertension is accompanied by sudden respiratory paralysis and deepening coma, but not by appreciable preliminary changes in pulse, respirations, or blood pressure (or by only short-lasting preliminary changes), the cerebellar tonsils are usually found to be wedged in the foramen magnum and the medulla to be severely compressed. If the primary cause of the pressure cannot be removed, suboccipital decompression is urgent, preceded by ventricular puncture during continued artificial respiration when necessary. To release the pressure on the medulla, it is necessary to remove the posterior arch of the foramen magnum—perhaps that of the atlas as well, and even that of the axis.

Rather characteristic of an acutely developing expanding lesion of the posterior fossa is a case of McIver's, cited by Campbell, Whitfield, and Greenwood.[5] A 13-year-old girl had sustained an injury to her head, without becoming unconscious.

> Two days after the accident she complained of headache and one day later began to vomit. On admission to the hospital four days thereafter, she exhibited no abnormal neurological findings. A few hours later there was sudden failure of respiration followed within 30 minutes by cessation of cardiac function. Autopsy revealed a partially liquid clot, about the size of a walnut, within the left cerebellar hemisphere.

Similar cases reported by Munslow[17] (extradural hematomas) show the tendency toward sudden respiratory paralysis in acute rapidly expanding infratentorial lesions. Sudden respiratory paralysis immediately followed lumbar puncture in the case of epidural hemorrhage in the posterior fossa reported by Beller and Peyser.[2] Autopsy disclosed the cerebellar tonsils herniated into the foramen magnum. There are similar reports in the literature.

In every case in which pulse and respirations steadily slowed down, whether blood pressure increased or not, we have found midbrain damage, usually accompanied by uncal herniation. In not every case of uncal herniation, on the other hand, did pulse and respirations slow down. It may be, to be sure, that uncal herniation and midbrain damage moderate the increases in pulse and respiration that accompany generalized acutely increased intracranial pressure, or that they are often accompanied by sudden drops in pulse and respiratory rates to subnormal levels.

Rising pulse and respirations and falling or unchanged blood pressure in the presence of the changes characteristic of midbrain damage may indicate (*a*) that compensation for the intracranial hypertension is failing and death is imminent or (*b*) that the patient is recovering. To read the signs rightly in a given case requires exhaustive study of the entire clinical picture. Take, for example, a patient in whom there is lessening of coma and, let us say, a lessening both of pupillary dilatation and of the signs of midbrain compression—such signs as decerebrate rigidity or opisthotonic fits or both.

In this case the inference is that intracranial pressure is falling and the patient recovering. But when coma is deepening, racing pulse, rapid respirations—possibly Cheyne-Stokes in type—and rapidly falling blood pressure may testify to severer cerebral compression, particularly of the midbrain, and may forecast death.

Certainly, observation of the pressure levels revealed by lumbar puncture should not be used as prognostic criteria, for, like many other investigators,[10,20] we have found patients with low cerebrospinal fluid pressure who nevertheless succumbed to the effects of markedly increased intracranial pressure. Lumbar puncture is therefore of little or no value in determining the level of intracranial pressure.

Indeed, it may in some hands be hazardous in patients harboring expanding brain lesions, since it may intensify or even precipitate uncal or cerebellar herniations and bring sudden death. Cushing believed that the pathogenesis of such serious effects of lumbar puncture was the abrupt removal of the external supporting cerebrospinal fluid pressure, leaving the intravascular pressure too great for the strength of the vessel walls. This mechanism may be in part responsible for the intracranial hemorrhages at times observed in some of these brains. In many cases, however, death is probably due to sudden compression of vital centers of the brain stem by uncal or cerebellar herniations suddenly thrust downward when the pressure in the supporting column of the spinal subarachnoid space falls precipitately.

Conclusions

1. In the experimental animal the changes in vital signs accompanying supratentorial compression are strikingly different from those accompanying infratentorial compression. With acutely expanding supratentorial masses, pulse and respirations become progressivly slower, blood pressure rises and its oscillations increase, and coma gradually deepens. Not so with acute infratentorial expansion, where direct compression of the medullary centers causes sudden death. To produce the above vital-sign changes characteristic of acutely expanding supratentorial lesions, it seems necessary that there be midbrain damage resulting either from uncal herniation through the tentorial hiatus or from transtentorial herniation of the brain stem or from both. The final link in the causal chain may be medullary anoxia.

2. In man deepening coma and a steady fall in respiratory or pulse rates or both, with or without a rise of blood pressure, implies severely increased intracranial pressure due to a supratentorial mass. The cause of the vital-sign changes is midbrain damage from transtentorial herniation of the midbrain or uncus or both. Removing the expanding lesion, making a large decompression on the side of the lesion, splitting the tentorium cerebelli, or reducing the herniation under direct vision is then urgent. Even without the vital-sign changes, however, and with or without uncal or midbrain herniation, severe intracranial hypertension may cause death.

3. In man, acutely expanding infratentorial lesions do not cause the Kocher-Cushing changes in vital signs. They do cause acute intracranial hypertension and are apt to produce sudden respiratory paralysis and coma either without preliminary changes in pulse, respirations, and blood pressure or else after very short-lasting increases or decreases.

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Morphology of the Neurosecretory Substances

A Study of the Human Hypothalamic Nuclei

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The principle of neurosecretion and the understanding of the hypothalamohypophysial interrelationship, although recently developed, are already well established and of great importance to several medical disciplines. Our knowledge about the function of this system is growing rapidly, but there is still much to be learned about the histology of the neurosecretory hypothalamic nuclei. The generally recognized concept of neurosecretion (Scharrer and Scharrer,[1] Bargmann,[2] Heller[3]) postulates that the neurosecretory hormones are produced by the nerve cells of the hypothalamic nuclei (supraoptic, paraventricular, and infundibular) and descend to the neurohypophysis along their neuraxes, which form the hypothalamohypophysial tract. The neurohypophysis has the mechanism for storage and the regulation of the release of this hormone.[4-6]

The histological visualization of the neurosecretory substance was made by previous investigators with chrome alum-hematoxylin-phloxine and aldehyde-fuchsin stains, which were developed by Gomori. This neurosecretory material, frequently referred to as the Gomori-positive substance, is present as granules or large droplets in the bodies of the ganglion cells and as thickenings of their neurites.

The modifications of the silver carbonate technique of del Río Hortega[7-9] has added new facts to our knowledge about the morphology of the neurohypophysis and hypothalamus. The present investigation was concerned with the determination of relationship between the Gomori-positive substance and the granules visualized with the silver techniques.

Material and Methods

The specimens for investigation were obtained from over 100 apparently normal brains removed in the course of routine necropsies. The ages ranged from newborn to 101 years. The hypothalami were fixed in brom-formalin (Cajal's solution) and then divided in the midline. One block was embedded in paraffin, and sections 4μ thick were stained with chrome alum-hematoxylin-phloxine (Gomori), aldehyde-fuchsin (Gomori), phosphotungstic acid hematoxylin (Mallory), periodic-acid leukofuchsin (Schiff), and occasionally by other methods. The other half of the hypothalamus was sectioned on a freezing microtome at 15μ and impregnated with several modifications of the silver carbonate method of del Río Hortega.

The modifications which were proved most successful in the visualization of the neurosecretory substances were those of Scharenberg's method for astroglia[10] and Hortega's triple technique. The brief outline for these two modifications is as follows: Sections are cut 15μ thick and placed in Cajal's solution.

1. Sections are washed briefly in distilled water to which a few drops of concentrated ammonia have been added.

2. Sections are washed in distilled water.

Technique 1.—The sections are allowed to remain in a solution of 50 cc. of Hortega's silver-carbonate weak (see below) with 60-100 drops of pyridine and twice this amount of absolute alcohol at room temperature and in darkness for three

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to eight days. The exact time must be determined by "fractionated" reduction and subsequent analysis of the slides under the microscope.

Unreduced Variant (U): 2. Sections are washed briefly in distilled water.

3. The sections are transferred into 0.2% gold chloride solution, in which they remain for one hour at 65 C.

4. Short washing in distilled water.

5. Fixation in 5% solution of sodium thiosulfate for 10 minutes. For better differentiation 5-10 drops of concentrated ammonia should be added to each 50 cc. of sodium thiosulfate.

6. Thorough washing in distilled water. Sections are then mounted, dried, and covered.

Reduced Variant (R): Step 1 is repeated.

2. Sections are transferred one at a time into 2% silver ammonia (see below) for 20 seconds.

3. Reduction in 1% formalin solution with 10 drops of pyridine per 250 cc.

4. Washing in distilled water.

5. Impregnation in 0.2% solution of gold chloride at room temperature for 20 minutes.

6. Brief but thorough washing in distilled water.

7. Fixation in 5% sodium thiosulfate, followed by the steps described previously.

Technique 2.—1. Sections are placed in 50 cc. of 2% silver nitrate solution with 6-100 drops of pyridine and twice this amount of nondenatured absolute alcohol for 24 hours at 65 C.

2. Sections are transferred directly into the Hortega silver carbonate weak solution, as described under Technique 1, followed by steps outlined in Technique 1 for the reduced or unreduced variant.

Silver carbonate weak solution is prepared by adding 275 cc. of distilled water to 100 cc. of stock solution. To prepare silver carbonate stock solution, 100 cc. of 10% silver nitrate is added to 300 cc. of 5% sodium carbonate solution; concentrated ammonia is added until the precipitate dissolves (avoid excess of ammonia). The solution is kept in a dark-brown bottle; this solution is good for six to eight weeks. Only clear solution is used.

To prepare 2% silver-nitrate ammonia, concentrated ammonia is added to 2% silver nitrate and stirred until the precipitate dissolves. Excess of ammonia is to be avoided. Only fresh clear solution should be used to avoid formation of fulminating silver.[11]

Description of the Material

The Gomori-positive material can be found occasionally in the ganglion cells of the human supraoptic, paraventricular, and infundibular nuclei. This substance may appear as droplets or as a large, confluent mass. In the Plate, *1-3* illustrate different types of ganglion cells from the supraoptic nucleus which show presence of Gomori-positive material. Some cells are filled to such an extent that their normal outlines are expanded. The corresponding picture in silver carbonate impregnation (Plate, *4*) shows two neurons with large masses of a darkly impregnated substance. An apparent enlargement of the cell body and of the neurite is shown in *5*. This resembles greatly the pictures of neurons with a large accumulation of the neurosecretory substance which has been demonstrated in the

1-3, neurons from supraoptic nucleus filled with various amounts of Gomori-positive substance. Chrome alum-hematoxylin-phloxine; reduced 10% of mag. × 1,000.

4 and *5*, neurons from supraoptic nucleus filled with neurosecretory material. Silver impregnation; reduced 10% of mag. × 1,000.

6, infundibulum. Fiber from hypothalamohypophysial tract containing Gomori-positive bead-like swellings. Chrome alum-hematoxylin-phloxine; reduced 10% of mag. × 1,000.

7, infundibulum. Accumulation of Gomori-positive neurosecretory material forming so-called Herring body. Chrome alum-hematoxylin-phloxine; reduced 10% of mag. × 1,000.

8, supraoptic nucleus. Neurite distorted in shape, due to the presence of neurosecretory material. Chrome alum-hematoxylin-phloxine; reduced 10% of mag. × 1,000.

9, stalk of neurohypophysis. Nerve fibers containing neurosecretory Gomori-positive material. Chrome alum-hematoxylin-phloxine; reduced 10% of mag. × 1,000.

10, neurohypophysis, posterior lobe. Accumulation of neurosecretory material. Chrome alum-hematoxylin-phloxine; reduced 10% of mag. × 1,000.

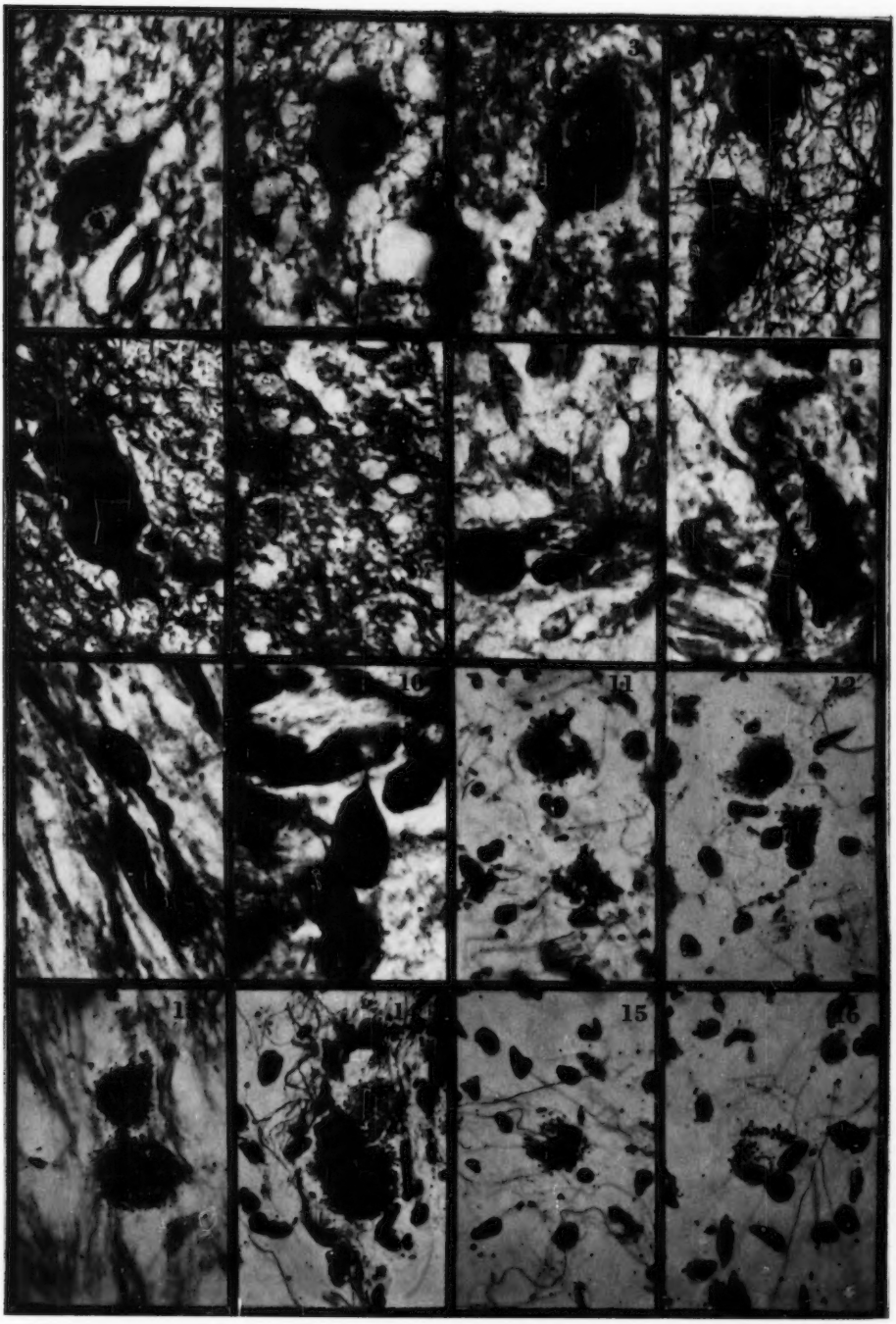
11, supraoptic nucleus. Cells filled with aurophil (upper cell) and argentophil (lower cell) granules. Silver impregnation; reduced 10% of mag. × 1,000.

12, supraoptic nucleus. Upper cell filled with aurophil granules. The cytoplasm and neurite of the lower cell are filled with argentophil granules. Silver impregnation; reduced 10% of mag. × 1,000.

13, supraoptic nucleus. Two cells filled with both argentophil and aurophil granules. Silver impregnation; reduced 10% of mag. × 1,000.

14, group of neurons from the supraoptic nucleus. Both types of granules can be distinguished, despite their abundance. Silver impregnation; reduced 10% of mag. × 1,000.

15 and *16*, neurohypophysis. Posterior lobe. Black (argentophil) and pink (aurophil) granules are accumulated around pituicytes. Silver impregnation; reduced 10% of mag. × 1,000.



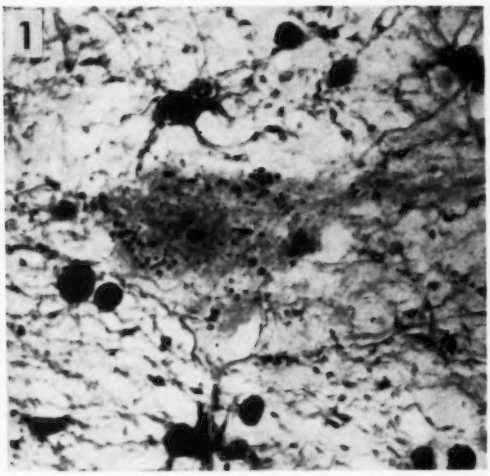


Fig. 1.—Neuron from the supraoptic nucleus with granules in the cytoplasm. Silver impregnation; mag. × 1,000.

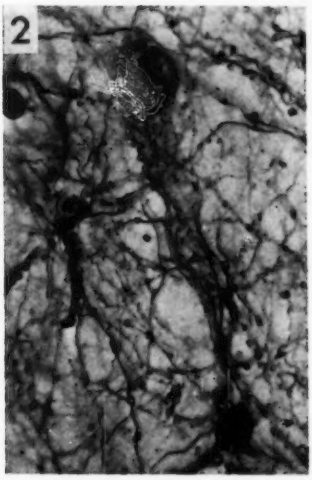
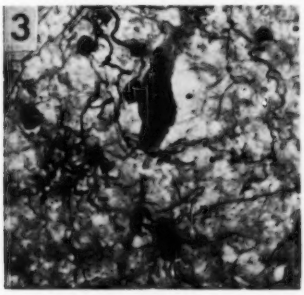


Fig. 2.—Paraventricular nucleus. Granules in the neurite. Silver impregnation; mag. × 1,000.

Fig. 3.—Infundibular nucleus. Granules in the cell body. Silver impregnation; mag. × 1,000.



literature.[12] A careful analysis of the darkly impregnated granules, in different nuclei, reveals wide variations. The granules, which are sometimes sparsely arranged, have a definitely different distribution and appearance from those of pigment, fat, or Nissl substance. Figure 1 shows a neuron from the magnocellular portion of the supraoptic nucleus, with small granules unevenly distributed in the cytoplasm and in the neurite. The smaller type of neuron from the paraventricular nucleus is shown in Figure 2. Very few granules are present in the cell body, but many are visible along the powerful neurite. The same type of small granules is found also in the cell bodies (Fig. 3) and along the neurites of the ganglion cells from the infundibular nucleus (Fig. 4).

Fig. 4.—Infundibular nucleus. Granules densely accumulated in the neurite. Silver impregnation; mag. × 1,000.

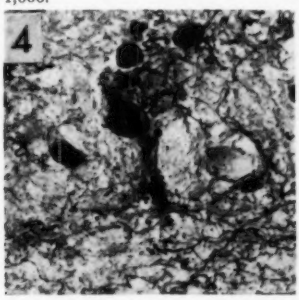


Fig. 5.—Supraoptic nucleus. Ganglion cell close to a capillary. Large granules are present in the cytoplasm. Silver impregnation; mag. × 1,000.

In some neurons, in addition to the argentophil granules, there are homogeneously impregnated argentophil black masses; in still others only the homogeneous masses are demonstrated. Figure 5 shows a neuron from the supraoptic nucleus close to a blood vessel. In one pole of this cell dark granules are concentrated, while the other pole is occupied by a darkly impregnated homogeneous mass. Some of the neurosecretory neurons located close together show great variety in the volume of the cell bodies and in the amount and distribution of the neurosecretory substance. In the group of neurons shown in Figure 6 the protoplasm of one ganglion cell is occupied by a large round vacuole (*A*); another cell (*B*) has its body and neurite filled with dark homogeneous substance, and the nucleus of the cell is barely recognizable. The cell at *C*

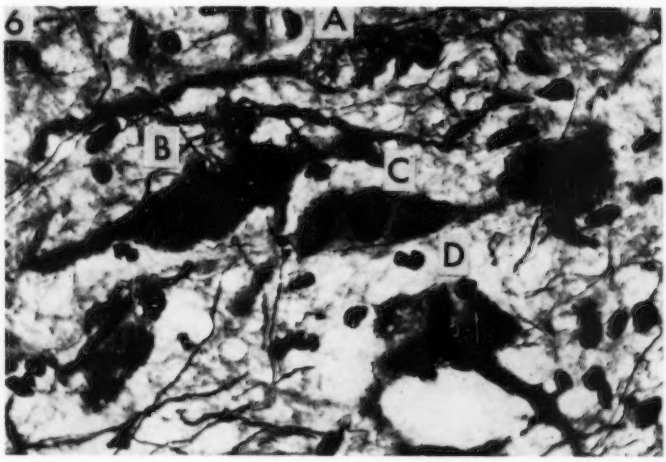


Fig. 6.—Supraoptic nucleus. Group of ganglion cells in apparently different stages of neurosecretion. (*A*) Cell with vacuole; (*B*) accumulation of neurosecretory substance, which expands the cell body and the neurite; (*C*) darkly impregnated material in both poles of the cell; (*D*) part of the cell body and neurite filled with neurosecretory material. Silver impregnation; mag. × 1,000.

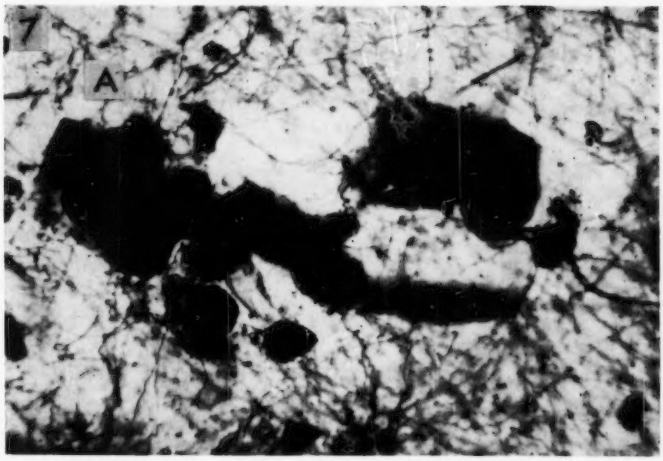


Fig. 7.—Supraoptic nucleus. Neurons with abundant neurosecretory material. Cell at *A* has a thickened neurite. Silver impregnation; mag. × 1,000.

shows both poles filled with a moderate amount of a darkly impregnated substance, but at *D* the neurite and the adjacent protoplasm are darkly impregnated. The two cells shown in Figure 7 are from the same nucleus supraopticus. The cell at *A* has a thickened neurite filled with a homogeneous, darkly impregnated substance in which a few granules are recognized; the other cell is homogeneously impregnated.

These findings obtained with silver carbonate impregnation correspond closely with the picture known from sections stained with Gomori's techniques. The granules which are positive can be followed along the neurites in the form of beads (Plate, *6*). Sometimes they produce marked thickening along the course of the nerve fiber (Plate, *7*). The neurons which produce them are sometimes distorted in shape, owing to an abundance of this material in the cell body (Plate, *8*). This material can be followed along the hypothalamohypophysial tract to the stalk (Plate, *9*) and to the neurohypophysis (Plate, *10*).

The impregnation of the neurosecretory substance with modified silver carbonate techniques presents a picture generally corresponding with the Gomori-positive substance and, in addition, permits a more detailed study of this material. On the basis of the results obtained with variants of the silver carbonate technique, the granules from the supraoptic and paraventricular nuclei and the nucleus infundibularis can be allocated to two types: (*a*) fine granules which stain pink or reddish (aurophil), and (*b*) coarse, relatively large black (argentophil) granules. In this particular variant the impregnation of cellular outlines was sacrificed in favor of visualization of the intracellular granules. There is no special segregation between the two types of granules; in the same field can be observed a cell filled with the aurophil granules and another cell filled with the argentophil type (Plate, *11*). In other fields can be observed accumulation of numerous pink and a few black granules (Plate, *12*, upper cell), and close to it, a cell filled with numerous coarse black granules which can be traced along the neurite (Plate, *12*, lower cell). In some cells there is present about equal amounts of the two types of granules (Plate, *13*). This technique almost always permits, even when the substance is densely accumulated, differentiation not only of the single granules but also of the type to which they belong (Plate, *14*).

These granules can, of course, be traced down along the hypothalamohypophysial tract to the neurohypophysis, where both types can be found in close relationship to the pituicytes (Plate, *15* and *16*).

Comment

To our knowledge, normal human material has never been investigated with silver methods which show specificity for the neurosecretory substance. The present study is an attempt at such an analysis.

Since the Gomori methods are accepted as the most sensitive equivalent picture of the neurosecretory substance, they have been employed as a "standard" for the silver-impregnated sections. Some pictures produced with the less specific variants of the silver impregnation are largely identical with those produced with Gomori's techniques and with those found by other investigators.[2,12] The substance which is produced by neurons appears either as granules (droplets) or as homogeneous masses and is present in the cell bodies and their neurites. The silver impregnation also concurs with morphological variations in these neurons, which apparently represent expressions of different stages of the neurosecretory function.[1,4,13]

The visualization of the two types of granules in the neurons of the neurosecretory nuclei is a new, but not an unexpected, finding. Green and van Breemen[14] analyzed the granules in the tractus hypophyseus as seen with the electron microscope and have found a difference between the granules in the tract and those in the neural lobe and Herring bodies. Of course, it is difficult to correlate their findings with ours, since different areas were examined and different techniques employed. D'Angelo[15] and associates have shown with conventional techniques results which permitted them postulation of two types of granules representing Gomori-positive substance. Lundberg,[16] in his investigation, disclosed the presence of three types of Gomori-positive substance in the human hypothalamus and neurohypophysis. These three types differ in distribution and in staining properties.

Since in the present investigation no animal experimental material was used, the evidence for the identity of the two types of granules described is indirect; we postulated the specificity of the Gomori technique for the neurosecretory substance and correlated our findings in silver impregnation with those obtained with Gomori's methods. This makes the correlation of the described histological picture with the production and release of neurohormones even more difficult, since Gomori's technique gives an equivalent picture of the neurohormonal activity in the histological sections, but is specific not for the neurohormone itself but only for the neurosecretory material which is closely associated with the neurohormone.[17,18]

The experimental work by Ortmann[19] established the identical behavior of the Gomori-positive substance and the neurohormone adiuretin. Since the synthesis of the active hormonal principle by du Vigneaud,[20] the nature of the octapeptide is definitely established. The hypothalamic nuclei are regarded as the place where they originate. Of course, the impulses which regulate their production in vivo are still under investigation. Experimentally, the function of the neurosecretory neurons can be influenced, for instance, by various amounts of parenteral doses of lipid fraction from the midbrain (Azzali[21]). The role of the cellular elements of the neurohypophysis, the pituicytes, remains controversial. Bargmann and Knopp,[22] in electron-microscope studies, found no direct evidence of presence of the neurosecretory substances in the pituicytes. Morphological evidence for a receptor and effector system which controls the hormone release has been described in the hypothalamic ganglion cells and in the neurohypophysis.

Labhart,[23] in his summary of our present knowledge, regards the carrier substance, the lipoglycoprotein, as combined with the active hormone, the octapeptide, and he considers the possibility that the entire complex is released into the blood stream, where the active polypeptides begin their function. He goes much further in his hypothesis when he states that the polypep-

tides formed in the hypothalamic nuclei are not only stored but also modified in the neurohypophysis. This is in accordance with the fact that in the dog there is a difference in the antidiuretic hormone (ADH)-oxytocin ratio in the hypothalamus and in the neurohypophysis, which may indicate a transfer of ADH (vasopressin) to oxytocin. These working hypotheses are very close to the findings described in the present paper. The described aurophil and argentophil granules, which represent two fractions of otherwise uniform Gomori-positive material, represent in a sense a histochemical visualization of two related but different principles. Very striking is the fact that these two substances show such variations in localization in the same hypothalamic nucleus. Granules of one type may fill out a neuron entirely, or may share it with the other type of granules. This histological picture represents various possibilities.

1. The two types of granules may represent the two known hormonal principles attached to their carriers. If the different stimulatory mechanisms are postulated for ADH and oxytocin, it would mean that the same neurons possess the mechanism to produce either hormone according to requirements. This method does not, however, permit differentiation of the substances in the hypothalamus and in the neurohypophysis and does not confirm the possibility of modification of the neurohormone in the neurohypophysis.

2. The second possibility is that one substance represents the hormone that is uniformly stained and the other a substance that represents an inactive material which under proper stimulation is changed into the active hormone; this could be true if the carrier substance could activate the prehormonal phase. Of course, the presence of both substances in the hypothalamus and in the neurohypophysis opens a possibility that the activation process does not occur only in the hypothalamus, which in a way would support Labhart's hypothesis of ambipotential qualities of the ADH. It is possible to assume that the ambivalent phase is not the active hormone itself but the undifferentiated precursor; and because the process of activation is not fully accomplished in the hypothalamus, it is obvious that varying demand for the different hormones will produce a different ratio between the oxytocin and the ADH in the hypothalamus and in the neurohypophysis.

3. Third, there is a possibility of a factor which may change the already active hormone into another. The relationship between the two hormones is very close, and clinical findings which are not yet fully investigated suggest an even closer relationship. The diabetes-insipidus mechanism[24] is relatively well understood and is related to the lack of ADH, which controls the resorptive activity of the distal kidney tubules. Polydipsia, as well as other symptoms of diabetes insipidus, is controlled by vasopressin (Pitressin) medication. The origin of polydipsia is still controversial. Some investigators believe that this results from polyuria. Others have been able to demonstrate that it appears independently and is controlled by a thirst center in the hypothalamus. The problem of polydipsia encompasses to some extent the area of activity of oxytocin which is believed to be the milk-ejecting principle. The breast stimulation which, in turn, is responsible for release of milk may frequently produce intense thirst, not different from that observed in diabetes insipidus but of short duration. This fact can be explained by (at least) an overlapping action of the two hormones, but the possibility that there is also present a substance which is capable of interchanging them cannot be discounted.

4. The control of the anterior lobe hormones by the hypothalamus is believed to occur through the portal system, into which the active substance must be released.[26] If this substance is in such a close relationship with other hypothalamoneurohypophysial hormones as the argentophil granules are with the aurophil granules, one of the two

may represent the anterior-lobe-regulating hormone.

All these listed hypothetical possibilities do not exhaust numerous mechanisms in which the two histologically defined substances may act. Despite the great contributions in recent years, the hypothalamohypophysial system remains terra incognita which will be charted not only by experimental work but also by careful investigation of clinical material, which undoubtedly will yield many answers.

Summary

With the use of the "fractionated" silver carbonate, pyridine-alcohol method, it is possible to distinguish in the Gomori-positive material two types of granules: (1) argentophil and (2) aurophil. These granules can be located in the same or in different neurons of the neurosecretory nuclei. The finding that the Gomori-positive substance in the histological picture obtained with fractionated silver carbonate impregnation appears as two substances—one argentophil, the other aurophil—suggests many implications and correlations with known physiological facts; but without proper biochemical study they will remain only hypotheses. Whatever the two different substances may represent in neurosecretory function, they are closely related to it, and the fact that we possess a specific and sensitive stain will make possible much better examination of the human pathological, and possibly animal experimental, material.

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Cerebral Paragonimiasis

A Report of Forty-Seven Cases

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Introduction

In Far Eastern countries, particularly Japan, Korea, China and Taiwan (Formosa), and the Philippines, the habit of eating raw crabs and other crustaceans is responsible for an endemic infection with the lung fluke Paragonimus westermani. The fluke, after leaving the cyst, pierces the intestinal wall to enter the abdominal cavity, whence it may perforate the diaphragm and penetrate the lung, either becoming encysted there or being carried to other organs. As a result of the pulmonary infection, the commonest symptom is hemoptysis. This is so common in these eastern countries that it is considered lightly. The diagnosis may be made in patients with a chronic cough and rusty-brown expectoration by a demonstration of the ova in the sputum.

Paragonimus infection of the brain, first reported by Otani,[10] of Japan, in 1887, is a frequent manifestation of the disease. Of 201 cases exhibiting extrapulmonary involvement, 93 had signs and symptoms suggestive of cerebral localization[12] (Table 1). The subject was discussed in a comprehensive review by Mitsuno and Zimmerman[8] in 1952, and more recently by Wang and Shih,[12] in 1956. In the 71 years that have elapsed since Otani first reported cerebral involvement, there have been many case reports based on postmortem examination, but only 21 instances of this complication have been demonstrated surgically.

The present paper is based upon 47 cases personally seen and examined; the diagnosis was made at the time of operation in 45 cases and at autopsy in 2 cases. Four of the cases in this series were previously reported; the rest are new cases.

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TABLE 1.—*Percentage of Cerebral Involvement in Paragonimiasis*

Author & Date	Cases	
	Extrapulmonary	Intracerebral
Ujima (1938)	36	18 (50%)
Nonomura (1941)	112	34 (30.3%)
Ko (1947)	95	35 (36.8%)
Wang (1956)	201	93 (46.3%)
Kim (1958)	162	98 (60.4%)

Incidence

Age and Sex Distribution of Cerebral Paragonimiasis.—In all series cerebral involvement is reported to occur predominantly in patients under 30 years of age, males being involved much more frequently than females (Table 2).

Social Status.—The majority of the patients came from the lower classes, with poor hygienic practices and little education (Table 3).

TABLE 2.—*Age and Sex Distribution of Cerebral Paragonimiasis*

Age, Yr.	No. Patients		
	Men	Women	Total
1 to 9	6	1	7
10 to 19	12	2	14
20 to 29	17	2	19
30 to 39	5	1	6
40 to 59	1	0	1
Total	41	6	47

TABLE 3.—*Education of Patients*

Schooling	No. Patients
None	24
Fourth grade	16
Middle school (Grades 7-9)	5
High school (Grades 10-12)	2

TABLE 4.—*Mode of Infestation*

	No Patients
Crab and crayfish	36
Raw fish	3
Contaminated water	2
Unknown	6

Mode of Infection.—Almost all of the patients gave a history of eating raw and poorly cooked crab and/or crayfish. Some apparently were infected through raw fish or impure water. The probable means of infection are given in Table 4.

Distribution of Paragonimus in the Body. Although paragonimiasis usually is present in the lungs, it may occur in other organs—intestine, liver, spleen, skin, etc.—without pulmonary infection. Such ectopic lesions of organs other than the brain are relatively benign, and rarely cause death. Patients with infection of these organs usually have a normal life span or die of some complicating disease. When cerebral infection occurs, the prognosis is grave, and death early in the course of the disease is likely. In some patients several organs may be infected besides the brain.

Symptomatology

Because people in the Orient regard hemoptysis, usually the first, and often the only, evidence of paragonimiasis, as an ordinary condition, pulmonary manifestations of the disease may be present for years before the patient consults a physician. Even cerebral symptoms may be present for years; patients in this series of 47 cases had complaints from 3 months to 18 years (Table 5).

Hemoptysis usually preceded any evidence of intracranial involvement, but at times (four cases) pulmonary and cerebral manifestations occurred at the same time, and in about one-third of the cases cerebral symptoms preceded hemoptysis. The time between pulmonary and cerebral manifestations is given in Table 6.

Matsumura[7] and others[2] noted that many patients had cerebral symptoms first and hemoptysis later. Initially the sputum of patients having cerebral paragonimiasis may be negative for the fluke, but later, even as much as two years, it may become positive. Busch[1] reported a patient having cerebral paragonimiasis whose sputum was negative preoperatively, but in which after a few months ova were found.

Seizures.—By far the commonest initial manifestation of cerebral paragonimiasis was a seizure (31 cases). The remainder of the patients, with two exceptions, had a seizure at some time in their course. Thus, 95% of the 47 cases had a convulsive

TABLE 5.—*Duration of Symptoms*

Time	No. Patients
0-3 mo.	4
3-6 mo.	7
6 mo.-1 yr.	7
1-2 yr.	7
2-3 yr.	5
3-5 yr.	3
5-10 yr.	8
10-15 yr.	4
More than 15 yr.	2
	—
	47

TABLE 6.—*Relationship of Hemoptysis and Signs or Symptoms of Central Nervous System Involvement*

Interval, Yr.	Hemoptysis Preceded Cerebral Signs	Cerebral Signs Preceded Hemoptysis
0-0.5	6	2
0.5-1.0	11	3
1.0-2.0	2	
2.0-3.0	2	4
3.0-4.0	3	
4.0-5.0	5	
5.0+		5

episode at some time during the course of the disease. One of the two patients without convulsions had lesions of the right cerebellar hemisphere and the other an occlusion of the right ascending frontoparietal artery. In 29 of the 45 patients many convulsive seizures occurred.

The type of seizure seemed to depend upon the localization of the intracranial lesion and the type of pathological condition found within the brain. In the majority of cases the patient gave a history of some type of paroxysmal minor impairment of neurological function which after a time developed into frank grand mal attacks. In many cases the minor episodes progressed to a focal seizure, and this seemed to correlate with other evidence of abscess formation. In 13 such cases the condition following this course. Patients with multiple cysts frequently had several types of convulsive episodes, including minor, focal, and grand mal seizures. This was prominent in nine of the cases. Patients with apoplectiform onset and no abscess usually had infreqeunt seizures.

Sudden Hemiplegia.—Sudden hemiplegia was the first symptom in six cases. In three other cases the sudden onset suggested embolism, and evidence of vascular occlusion was found at the time of surgery.

Meningitic Syndrome.—In six cases the predominant symptoms were those of chronic meningitis, with headache, stiff neck, vomiting, and fever. Severe headache associated with papilledema was noted in seven cases, but other patients complained of mild headache from time to time. Fever was noted in eight patients, the temperature usually being not higher than 102 F.

Mental Retardation.—Feeblemindedness has been attributed to cerebral paragonimiasis by Hooper,[3] Lee,[6] Matsumura,[7] and Jinnai,[4] as well as Mitsuno and Zimmerman[8] and Wang and Shih,[12] a state confirmed by this study, for only four cases of this series had normal mental development.

Physical Findings

General Examination.—Practically all the patients had evidence of a generalized debilitating condition. In all 47 cases roentgenograms of the chest were positive for pulmonary paragonimiasis. Nine patients had a complicating pleural effusion. In the aspirated fluid ova were found in five cases, and an adult fluke and ova, in another case at thoracotomy. The pus from the pleural cavity contained as high as 89% eosinophils but was not proteolytic. Usually patients with a pleural effusion due to Paragonimus had little fever and recovered upon thoracocentesis.

The organism occasionally involved other structures. In one case (Case 12) an adult fluke was found in the left inguinal lymph node. In another patient a cyst was present in the subcutaneous tissues near the umbilicus. In one case the spinal cord was involved.

Neurological Examination.—Only five patients in this series had a normal mental status. Personality changes had occurred in 11 and mental deterioration sufficient to prevent work in 14 patients. Nine children were so mentally retarded that they could not attend school. One boy, having the intelligence of an idiot, had seizures at the age of 7 years and developed hemoptysis eight years later. Two patients had severe amnesia and were seriously disoriented; in these cases chronic arachnoiditis with abscess and cyst formation was present. Four patients were admitted in a drowsy state, and one was semicomatose.

Cranial nerve involvement was frequently found, as Table 7 indicates. Papilledema was present in only seven cases.

Other patients had symptoms of intracranial pressure temporarily as an abscess

TABLE 7.—*Cranial Nerve Involvement*

Cranial nerve	1	2	3	4	5	6	7	8	9	10	11	12
Number involved	9	2*	13	0	1	4	33	8	8	10	0	9

* Two patients were blind, and nine had a homonymous hemianopsia.

TABLE 8.—*Visual Acuity Impairment*

Visual Acuity in Cerebral Paragonimiasis	No. Cases
Blind	2 (4.2%)
Under 20/40	21 (44.7%)
20/20-20/40	15 (32%)
Above 20/20	9 (19.1%)

TABLE 9.—*Blood and Spinal Fluid*

	Mean	Variation
Blood		
Hemoglobin	11 gm.	8-14 gm.
White blood cells	8,400/cu. mm.	4,500-15,500/ cu. mm.
Eosinophils	14%	1%-51%
Cerebrospinal fluid		
Cells		
Lymphocytes	16/cu. mm.	3-165/cu. mm.
Leukocytes	3.3/cu. mm.	0-25/cu. mm.
Pandy reaction	+	0 - +++

formed, but did not have papilledema. In three cases the papilledema was due to obstruction in the ventricular system from abscesses of the cerebellum. Although choked disks are present in from 50%-70% of patients having brain tumors, in cerebral paragonimiasis the incidence of papilledema was found to be as low as 14.9%. Visual acuity was impaired in the majority of the patients (Table 8). Pupillary alterations were common, being usually in the form of impaired reaction, but anisocoria was present in eight patients.

Some weakness on one side was present in 37 patients, usually associated with increased reflexes, a positive Babinski sign and, in five cases, forced grasping. In two patients a quadriparesis was noted.

Sensory disturbances on the involved side in the form of hypesthesia were found in 28 patients and of astereognosis in 13 patients.

Signs of meningeal irritation were prominent in 11 patients and of cerebellar involvement in 3 patients.

Laboratory Data

Urinalysis was normal except for traces of albumin in three patients with fever.

Sputum examination of all patients was positive for Paragonimus ova and negative for tubercle bacilli (for both on smear and culture).

The blood and spinal fluid findings are given in Table 9.

During abscess formation patients had an increasing cell count in the spinal fluid,

Fig. 1.—Roentgenogram of the skull of a 12-year-old boy who had had symptoms of paragonimiasis for seven years. The multiple calcified cysts are well visualized.

with a positive Pandy reaction and increasing eosinophils in the blood and spinal fluid. The globulin reaction of the spinal fluid often reflected the state of the patient's condition, being higher as the general state worsened.

In roentgenographic examinations of the chest, 38 patients (80.8%) had a cyst or pneumatocele in the lung parenchyma, and 9 patients had pleural effusion.

Patients having cerebral abscess due to Paragonimus with a long clinical history usually had a calcified shadow in the x-rays of the skull (Fig. 1). On the other hand, patients with miliary granulomatous arachnoiditis did not show calcification in the x-ray of the skull, even though they had a long history.

Of the 47 cases in this series, 18 had calcified shadows in the x-ray of the skull, the degree of density roughly correlating with the duration of symptoms. Although these 18 patients had presumably had pulmonary paragonimiasis for an equally long time, they did not have calcified lesions in the lung, with the exception of Patient 32, who had a solitary calcified paragonimiasis cyst, verified post mortem.

Ventriculograms in 14 cases with brain abscess revealed displacement or filling defect of the ventricular system; in one case hydrocephalus was noted. Pneumoencephalography was performed in 16 cases, revealing insufficient air filling in the subarachnoid space and deformity of the ventricular system. Tomograms of the skull were made in 12 cases having calcified shadows on the plain film. These special roentgenograms were of great help in localizing the site of the calcification.

Diagnosis

The diagnosis is usually suggested by the history of hemoptysis in a young peasant who lives in a country where paragonimiasis is endemic and who has had some mental impairment and symptoms of cerebral involvement, such as convulsions or a stroke. The finding of ova or the fluke in sputum or stool will confirm the diagnosis. The complement-fixation test may help. Eosinophilia in the blood should raise the suspicion of paragonimiasis in an Oriental person. Roentgenograms of the skull and chest usually show typical lesions. The differential diagnosis should include, besides these parasitic diseases, brain tumor, stroke, brain abscess, tuberculous meningitis, and encephalitis.

Pathological Anatomy

Within the central nervous system, the reactions to the fluke take one or some combination of three forms: (1) chronic arachnoiditis, (2) granuloma, and (3) encapsulated abscess. In fatal cases all three of these pathological changes may be seen usually, but at surgery a solitary lesion may be found.

Chronic Arachnoiditis.—This reaction may be of any degree, but it is a response to the presence of ova in the subarachnoid space, although they may be sparse and difficult to find. The cellular response is usually lymphocytic, although leukocytes may be seen and phagocytic cells are common. The connective tissue reaction may be prominent, with relatively few cells (Fig. 2), or the subarachnoid space may appear granulomatous. There is often a marked endothelial thickening of the small arteries.

Granulomas.—Granulomas may be found in the cerebral parenchyma as isolated masses, or they may be related to softenings of the cortex or subcortex. The granuloma surrounds a few ova and is composed of cellular masses on a loose connective tissue base. The cells are predominantly lymphocytes, but polymorphonuclear leukocytes and phagocytes are also present. Giant cells are rarely seen (Fig. 3).

Encapsulated Abscess.—The abscess may be superficial or deep in the cerebral tissue, but has a typical appearance. About the relatively thin connective tissue capsule are a few layers of xanthomatous-like cells, with or without small round cells. Inside the thin hyalinized connective tissue capsule is a varying number of ova, many of which

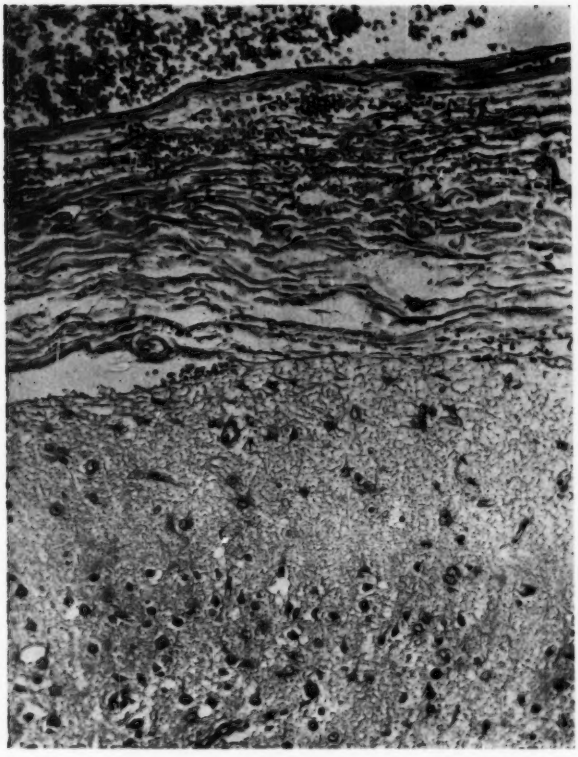

Fig. 2.—Chronic arachnoiditis over the cerebral cortex secondary to Paragonimus infection of the brain. Hematoxylin and eosin; × 150.

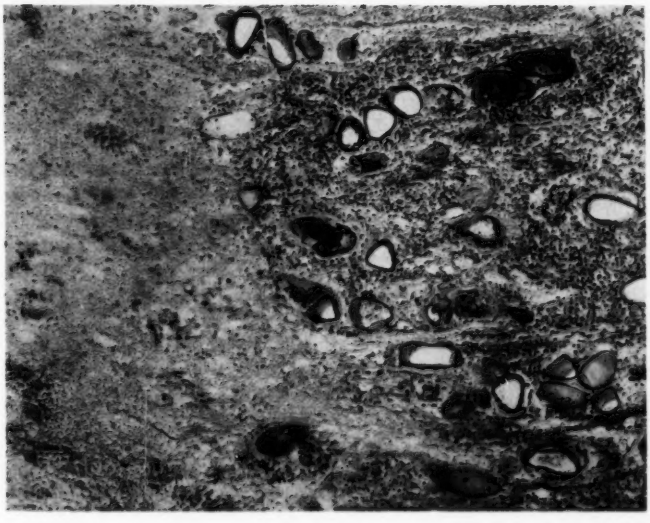

Fig. 3.—Chronic granuloma with multiple Paragonimus ova. Hematoxylin and eosin; reduced to 88% of mag. × 125.

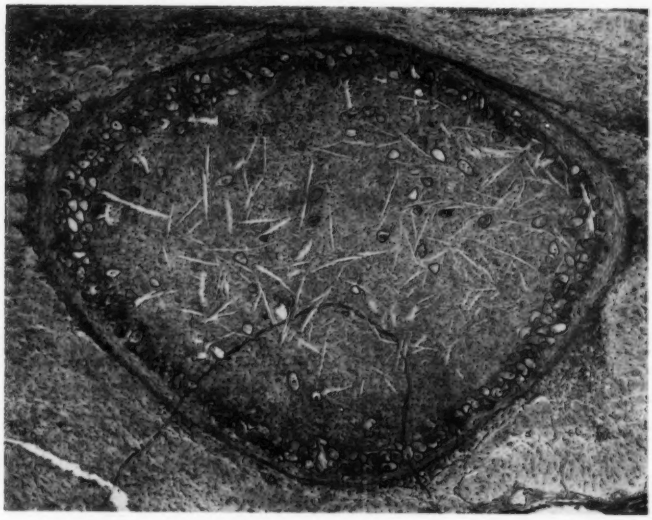

Fig. 4. — Paragonimus cyst in the cerebral hemisphere; within the capsule many ova are present. Hematoxylin and eosin; reduced to 88% of mag. × 40.

consist only of the shell, without yolk or egg. Inside this layer is necrotic cellular debris, with clear slits suggesting cholesterol crystals. These abscesses may contain an adult worm and may be shelled out of the tissue. They attain a diameter of 1-2 cm. (Fig. 4).

Occasionally the fluke will be found in a large vessel or venous sinus (four cases).

Treatment

Medical.—In this series nine patients were given emetine and antimony sodium tartrate (Stibnal), resulting in a discharge of ruptured ova in the sputum. The cerebral symptoms were not improved. In patients so treated the pus from the cerebral lesions contained only the shell of the ovum, without a yolk. This has been noted in the sputum previously by Ujima,[11] in 1938.

Surgical.—In general, surgical intervention was reserved for the removal of localized abscesses or granulomas due to Paragonimus. In such cases the results were good. In chronic multiple infections or generalized arachnoiditis, surgical therapy was of little value. On the basis of the experience gained from the study of this series of cases, the following criteria favored the presence of a localized process suitable for surgical excision:

1. Irritative or paralytic manifestations of a single cerebral lesion of short duration or, if of longer duration, with a recent exacerbation of symptoms
2. Frequent focal fits associated with signs of increasing intracranial pressure
3. Increasing leukocytosis and eosinophilia in blood and cerebrospinal fluid
4. A single cerebral lesion in plain roentgenograms of the skull or in ventriculograms

The following criteria indicated multiple or diffuse lesions and were unfavorable prognostic signs for surgical therapy:

1. Clinical manifestations or radiological evidence of multiple intracerebral lesions
2. Long history of diffuse cerebral involvement without an acute phase (probably indicating arachnoiditis)
3. Generalized seizures without focal manifestations
4. Apoplectiform onset of symptoms

Surgical resection of the cerebral abscess often relieved the convulsive episodes, although some patients continued to have less frequent minor seizures. If the brain abscess was not surgically removed, even though it became calcified or well encapsulated, generalized seizures persisted for long periods. In 10 patients such multiloculated, firm cysts, with necrotic brain tissue and gliosis about the cyst, were found at

TABLE 10.—*Result of Surgery*

	No. Cases
Cured	6
Improved	8
Unchanged	24
Worse	3
Died	4
Died before surgery (autopsy)	2

the time of surgical intervention. Focal and generalized seizures occurred early in nine cases of multiple cysts without surrounding reaction, but tended to diminish in frequency. In seven patients with chronic arachnoiditis and numerous small nodules in the thickened arachnoid, grand mal seizures occurred from the onset of the cerebral manifestations. In eight patients a living fluke was found inside the abscess cavity; all had frequent focal seizures. In seven patients in whom seizures were infrequent prior to surgery, no fluke was found in the abscess cavity. In some eight cases the convulsive manifestations cleared up completely after operation for periods of from two months to three years.

Surgical intervention is for the evacuation or excision of abscesses, or the removal of granulomas. It is carried out through an appropriately placed osteoplastic craniotomy, made under general anesthesia. After the dura mater is opened, the diseased cerebral tissue is removed if in an area in which an excision may be carried out without producing severe neurological deficits. An abscess may be evacuated and its capsule shelled out if a more radical resection seems inadvisable. The dura mater is usually closed tightly and the bone flap replaced.

In Table 10 the results of surgical therapy are presented.

Summary

The incidence of cerebral paragonimiasis is discussed in terms of age, sex, social status, and anatomical distribution.

Cerebral infection is characterized clinically by epileptic manifestations and meningitic or apoplectic signs.

The lesions may consist of chronic arachnoiditis, local granulomas, or encapsulated abscesses, frequently containing the fluke.

In cases in which the lesions are localized, surgical excision offers a good chance for relief of the epilepsy and arrest of the cerebral disease; in diffuse and multiple lesions surgery has little to offer.

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Cerebral Vasospasm in Angiography for Intracranial Aneurysms

Incidence and Significance in One Hundred Consecutive Angiograms

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The concept of spasm of the cerebral arteries is of particular importance as regards its relationship to ruptured intracranial aneurysms. Vasospasm has long been suspected as a cause of cerebral ischemia in a variety of conditions, but proof of its occurrence in the human subject has been particularly difficult to obtain, for reasons that are obvious. The uncritical use of the term "vasospasm" as an explanation of cerebral ischemia in vascular disease of the brain has been rightly criticized by Denny-Brown [1] and others. Pickering [2] was of the opinion that true spasm is a rare condition. However, since the advent and widespread usage of cerebral angiography in the diagnosis of subarachnoid hemorrhage, it has become evident that spasm of the major cerebral arteries not infrequently occurs after the rupture of an intracranial aneurysm. Direct observation of the constricted vessels at surgery has been reported with increasing frequency since the intracranial approach to eradication of these lesions has become commoner. There are also indications that the clinical course following rupture of an aneurysm may be dependent to a large degree upon the presence, extent, and duration of such spasm.

Historical Review

In 1902 Bayliss [3] found that a peripheral arterial vessel would respond by constriction to a sudden direct increase in intra-arterial pressure.

An arteriographic demonstration of experimentally produced spasm of the femoral arteries in rabbits was published by Barnes and Trueta [4] in 1942. In the same year Egas Moniz [5] presented a case of transitory hemiparesis and aphasia which he considered to be due to cerebral arterial spasm. A temporary block was demonstrated in the internal carotid artery at angiography. Ecker,[6] in 1945, demonstrated the presence of cerebrovascular insufficiency due to spasm of the internal carotid artery in three soldiers with "near-miss" missile injuries of the neck.

Robertson [7] reported on cerebral lesions due to intracranial aneurysms and concluded that ischemic lesions in patients with ruptured aneurysms were occasionally due to arterial spasm and that "it is probable that this mechanism is far commoner than realized." Poppen [8] noted that the peripheral cerebral arteries are at times in spasm from trauma to the arterial wall by the rupture of an aneurysm and the resulting perivascular extravasation of blood.

Ecker and Riemenschneider,[9] in 1951, demonstrated spasm of the major cerebral arteries by comparative arteriograms in seven instances occurring in six aneurysms of or near the circle of Willis. Norlén and Olivecrona [10] stated that an intense vasoconstriction was nearly always present in the cerebral arteries shortly after hemorrhage from a ruptured aneurysm and considered this vasoconstriction to be a protective mechanism to prevent further

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hemorrhage. They noted that this vasoconstriction is almost never observed in cerebral arteries in conditions other than aneurysms, and that it occurs in the latter only when there has been recent hemorrhage. Logue [11] indicated that vascular spasm may be responsible not only for the arrest of hemorrhage but also for the initial coma and death (in cases in which at necropsy no intracerebral clot is found) and, to a large extent, the neurological damage. Recently, moreover, spasm has more frequently been mentioned as a complication of ruptured intracranial aneurysm.[12-16]

The relationships between cerebral vascular spasm and these ischemic lesions have never been adequately investigated, so that the mechanism of their pathogenesis remains conjectural. However, current laboratory studies promise to elucidate some aspects of the problem.[17]

Purpose and Methods of Present Investigation

The present study is concerned with the clinical implications of cerebral vasospasm as determined by angiography. We believe, as others have indicated, that spasm of the internal carotid artery or its major branches is a common accompaniment of ruptured intracranial aneurysm and that the patient's clinical course may be dependent to a large degree upon the presence, extent, and duration of this spasm. As a pathogenic mechanism, it may result in localized or generalized insufficiency of the cerebral circulation, thereby producing ischemia of varying degrees in the involved areas of distribution. Recognition of the occurrence of spasm may be of considerable value to the neurologist and the neurosurgeon alike, particularly as to prognosis and as a guide to management, and occasionally in diagnosis or localization.

For the purposes of this study the cerebral angiograms of 100 consecutive cases of intracranial aneurysm were reviewed and correlated with the clinical history, findings, and course.

Up to 1957 it was the policy of the neurological and neurosurgical services at the Neurological Institute of New York to carry out angiography after the patient's clinical condition had become stable and there were no signs of continued or new bleeding. In only one-tenth of the patients in this series was angiography carried out before the fifth day. It was not thought that angiography altered the course of the disease except in four cases, in which the patient's condition became worse following the procedure, and only two of these demonstrated spasm.

Angiography was performed using percutaneous puncture of the common carotid artery, and serial films were made by identical roentgenological techniques.

By spasm we mean a narrowing of the lumen of the vessel beyond that which we considered a normal anatomical variant. The narrowing involved the intracranial arteries almost exclusively, the cervical portion being rarely affected. In the case of the anterior cerebral artery, where hypoplasia is a common anatomical variant, narrowing was not considered spasm unless a local segment only was involved. In the case of the supraclinoid portion of the carotid siphon, narrowing was not considered significant unless its diameter was less than two-thirds the size of the intracavernous portion, as measured on the films. In 100 normal carotid angiograms the diameter of the supraclinoid portion of the carotid was always two-thirds or more that of the intracavernous portion (Fig. 1).

On examination of the arteriograms, spasm was found to be local or diffuse. By local spasm we mean a constricted area of the vessel 1-2 cm. proximal or distal to the aneurysm, whereas diffuse spasm was more extensive. In this series of 100 cases there were 39 cases of spasm, of which 6 were local and 33 were diffuse. The spasm was usually noted on the same side as the bleeding aneurysm, although in six patients it occurred bilaterally (Fig. 2).

Spontaneous subarachnoid hemorrhage occurred in 85 of the 100 cases prior to the

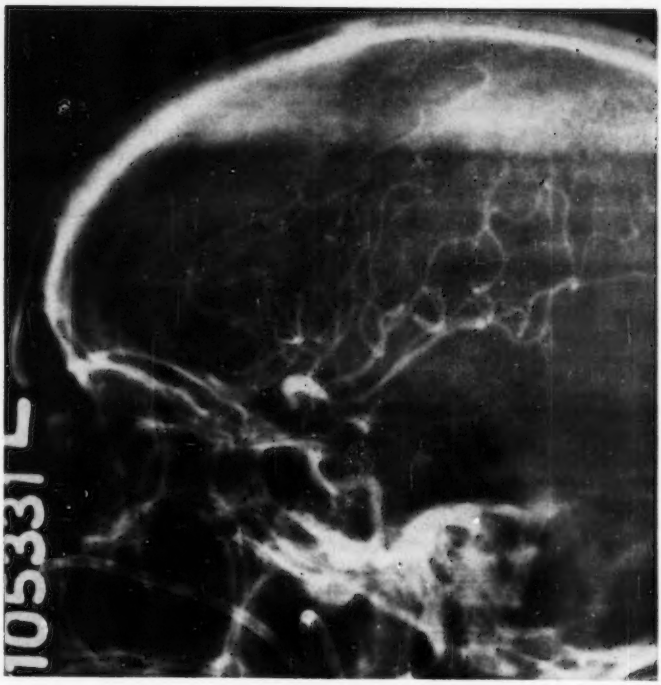


Fig. 1.—Lateral view, left carotid arteriogram, 10 days after spontaneous subarachnoid hemorrhage, showing an aneurysm of the anterior communicating artery. There is marked spasm of the supraclinoid portion of the internal carotid artery and proximal portion of the middle cerebral artery. Note the difference in caliber between the supraclinoid and the intracavernous portion of the internal carotid artery. This patient had no localizing signs upon admission and showed apparent improvement until the sixth day after onset, when she developed hemiparesis and aphasia, although spinal fluid showed clearing of blood.

time of angiography; in the remaining 15 cases, the aneurysm was an incidental finding, or the patient had neurological signs and symptoms suggesting aneurysm with no history of bleeding. All of the patients showing vasospasm, however, had had an episode of bleeding, with one exception, in which focal narrowing was found involving

Fig. 2.—Diffuse spasm disappearing three weeks later.

A is an anteroposterior view, left carotid arteriogram 20 days after onset of spontaneous subarachnoid hemorrhage from an aneurysm of the anterior communicating artery. One week after onset of bleeding the patient developed right hemiplegia. This figure shows marked diffuse spasm of the internal carotid artery (supraclinoid portion) and of the anterior and middle cerebral arteries.

B, taken three weeks after *A*, shows normal caliber of these vessels.

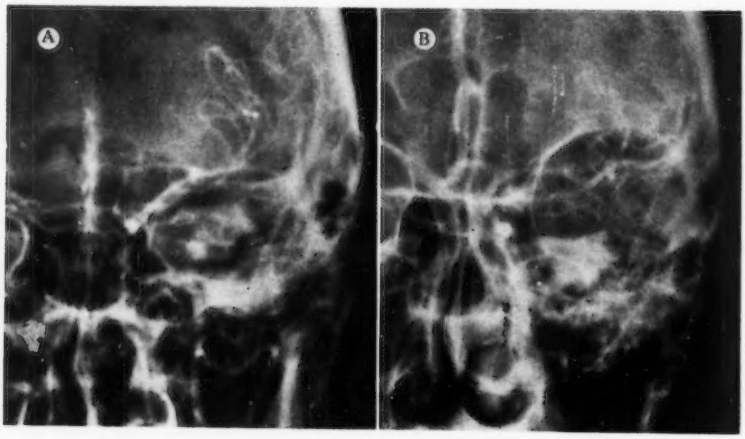


TABLE 1.—*Incidence of Spasm by Age in One Hundred Consecutive Patients with Intracranial Aneurysm*

Age	Cases With Spasm	Cases Without Spasm	Total
11-20	1	1	2
21-30	4	4	8
31-40	8	13	21
41-50	22	16	38
51-60	3	20	23
61-70	1	7	8
Total	39	61	100

the internal carotid artery adjacent to a pituitary adenoma.

A number of interesting features became evident upon making comparisons of the 39 cases showing spasm and the 61 cases without spasm.

Age Incidence

Table 1 shows the incidence of spasm as related to the age of the patients. The incidence in the two groups showed an approximately equal distribution up to the age of 50, after which the incidence of spasm dropped off sharply, although a third of the total number of patients were over 50 years of age. The average age of those showing spasm was 41, as compared with an average age of 47 for the group without spasm. The ages of the group with spasm ranged from 14 to 63.

Of interest in this connection was the absence of spasm in the nine patients in this series who presented localized changes in the carotid arterial system thought to represent arteriosclerosis. These findings included tortuosity, irregularity, calcifications, and narrowing or irregular widening of the lumen. They were noted primarily in the carotid siphon, but involved also in some cases the adjacent portions of the internal carotid artery and its major branches. In none of these patients was vascular spasm demonstrated, although it might have been expected in eight of them who had had recent episodes of subarachnoid hemorrhage. The average age in this group was 57. The absence of spasm in

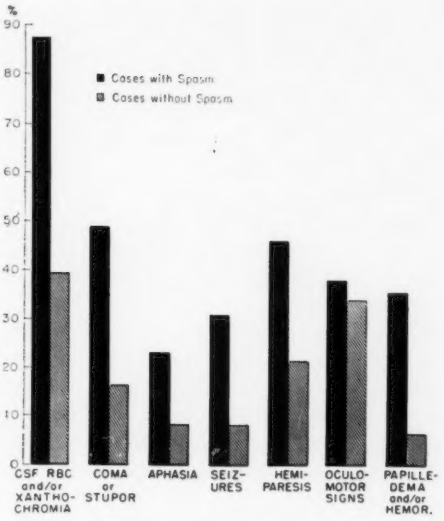


Fig. 3.—Incidence of positive signs in cases with and without spasm.

all of these 9 older patients suggests that arteriosclerosis may have prevented its occurrence.

Incidence of Neurological Signs

Certain clinical findings were more prevalent in cases with spasm than in those without. For example, the incidence of coma or stupor, aphasia, seizures, hemiparesis, and papilledema was significantly greater in the patients showing spasm. Figure 3 shows the clinical findings present at the time of arteriography. In the presence of spasm, coma or stupor occurred three times, aphasia two times, seizures three times, hemiparesis two times, and papilledema five times as frequently as in the absence of spasm. The incidence of oculomotor signs in the two groups was approximately the same, whereas visual field defects, when obtainable, were more commonly seen in patients without spasm. These findings are in keeping with the fact that several of the patients who did not have vascular spasm presented themselves with eye signs as their initial complaint and gave no history of subarachnoid bleeding. The aneurysm, moreover, was an incidental finding in five

TABLE 2.—*Spinal Fluid Examination Prior to Angiography in One Hundred Consecutive Patients with Intracranial Aneurysm*

	Cases With Spasm	Cases Without Spasm	Total
Spinal fluid			
Grossly bloody	23	7	30
1+ blood with xanthochromia	6	6	12
Xanthochromia	3	6	9
Clear	4	9	13
History of bleeding with no recent lumbar puncture	2	19	21
No history of bleeding	1	14	15
Total	39	61	100

of the patients without spasm, as compared with local spasm or narrowing in a patient with a pituitary adenoma in addition to the aneurysm.

The spinal fluid findings of the patients in this series just prior to arteriography are given in Table 2. Eighty-seven per cent of the patients with spasm had bloody or xanthochromic spinal fluid at that time, as compared with only 31% without spasm who had bloody or xanthochromic spinal fluid. These findings indicate that the presence of blood in the spinal fluid is correlated with the finding of spasm.

On the other hand, spasm may occur or increase despite clearing of blood from the cerebrospinal fluid and apparent improvement in the patient's clinical status. Three patients in this series, for example, developed aphasia and hemiplegia five days (two cases) and two weeks following episodes of subarachnoid bleeding, after which their spinal fluid had cleared and they were thought to be improving. Even though "late" hemiparesis and aphasia had developed, repeated lumbar punctures still revealed no evidence of recurrent hemorrhage. In two of these cases, in which autopsy was performed, there was no evidence of hematoma, thrombosis, or intracerebral rupture. Encephalomalacia, however, was found in the areas of distribution of the vessels in spasm.

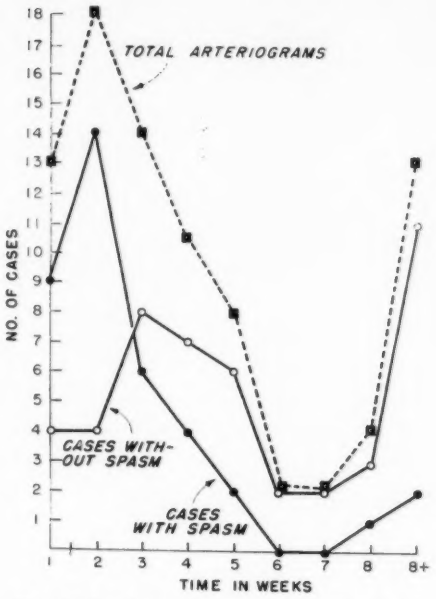


Fig. 4.—Incidence of spasm as related to time from presumed rupture to arteriography.

Time Interval

In an effort to estimate the approximate time of appearance and the duration of vasospasm in these cases, the time interval from rupture of the aneurysm to angiography was determined. Of the 38 patients showing spasm following aneurysmal rupture, 29 (76%) were studied within three weeks of bleeding.

In Figure 4 the two groups of patients are compared according to this time interval. Of those with spasm, 9 (23.7%) had angiography within one week of bleeding; 14 (36.8%), within the second week; 6 (15.8%), within the third week, and 4 (10.5%), within the fourth week. The average interval in this group was 13 days. In the group without spasm, 4 (8.5%) were studied within the 1st week, 4 (8.5%) within the 2d week, 8 (17%) within the 3d week, 7 (14.9%) within the 4th week, and 24 (51%) more than 4 weeks later, with an average of 28 days for the group.

In two patients vasospasm was found within 24 hours of the time of rupture.

It is therefore to be expected that spasm would frequently be found sooner after aneurysmal rupture if angiography were carried out at an earlier date.

Disappearance of spasm, as determined by follow-up angiography, was found in 14 patients of this series on repeat examinations made at intervals of nine days to five months after initial films had shown spasm. In one patient with a moderate degree of vasospasm involving the right internal carotid (supraclinoid portion) and middle cerebral arteries there was marked improvement of the spasm on repeat arteriography five days later, whereas a third angiographic examination, three months thereafter, showed that the previously involved vessels were now of normal caliber. Several other patients also showed clearing of vasospasm two to three weeks after rupture of their aneurysm.

Mortality

As shown in Table 3, the mortality rate was greater in the group of patients showing spasm, particularly during the first three weeks following bleeding. Of the 29 patients in whom spasm was demonstrated, 12 died, and 11 of these died within the first three weeks following rupture of the aneurysm. Of the 61 patients without spasm, 10 died. One died of metastatic carcinoma, and another, who had presented with progressive visual difficulty but no history of subarachnoid bleeding, died soon after cervical ligation of the common carotid artery. Three of these patients showed arteriosclerotic changes in the carotid arterial system. Three also died after recurrent bleeding episodes, after which there was no opportunity to repeat angiography.

TABLE 3.—*Mortality in One Hundred Consecutive Patients with Intracranial Aneurysm*

Deaths	Cases With Spasm	Cases Without Spasm
Within 3 wk	11	4
From 3d to 8th wk	1	2
After 8 wk	0	1
Total	12	7

Extent of Spasm

The clinical course and findings appeared to be related to the severity and extent of arterial spasm. There were 27 patients with diffuse unilateral spasm following aneurysmal rupture, and of these, 8 died, 4 were completely disabled, and 3 had major neurological deficits.

The six patients with bilateral spasm presented the following findings: hemiparesis and coma, three; aphasia and papilledema, two, and oculomotor palsy, three. Of this group, four died.

Local spasm was found in six patients of this series, and five of these had had subarachnoid bleeding from 12 to 53 days prior to angiography. The one patient without a history of bleeding had a pituitary adenoma with acromegaly in addition to an aneurysm at the origin of the posterior communicating artery. Two of this group presented with oculomotor signs. Three made a complete recovery; two recovered with minimal deficit (partial III nerve paralysis), and one had hemiparesis.

These findings indicate that the prognosis is better when the extent of spasm is less.

Occurrence of Spasm

Spasm which occurs after the rupture of an intracranial aneurysm affects the vessels in continuity with the aneurysm and may extend in a proximal or in a distal direction. In severe cases of spasm, arterial filling on the involved side may be minimal (Fig. 5). Similarly, the blood flow as determined on serial arteriograms apparently may be markedly slowed.

There appears to be no relationship between the presence of spasm and the site of ruptured aneurysm except that the occurrence of bilateral spasm was more frequently seen with aneurysms of the anterior communicating artery. *No arterial spasm was seen in association with infraclinoid aneurysms.*

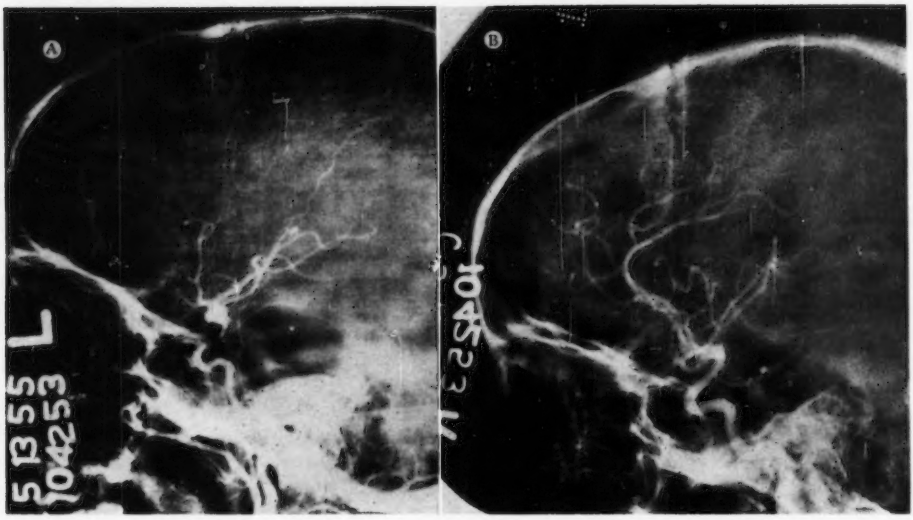


Fig. 5.—Lateral views of bilateral carotid arteriograms made at the same angiographic sitting.

A shows the left side, with an aneurysm at the bifurcation of the internal carotid artery and spasm involving the anterior cerebral artery, proximal portion of the middle cerebral artery, and the supraclinoid portion of the internal carotid artery.

B shows the right side, in which the arterial filling is normal.

Fig. 6.—Lateral view, right common carotid arteriogram, showing aneurysm of anterior communicating artery. Local spasm of pericollosal artery distal to the aneurysm, which might be overlooked on casual inspection.

Although it usually occurs on the side of the aneurysm involved, vascular spasm was found only on the side opposite to the site of origin of a large internal carotid artery aneurysm in one patient in this series. The aneurysmal sac extended across the midline, and the suspected site of rupture, seen as a defect in the sac outline, lay immediately adjacent to the segment of the internal carotid artery involved by spasm.

The presence and location of local spasm may be the only clue to the site of a ruptured aneurysm when multiple aneurysms are present or when an aneurysm fails to fill on initial angiography.[15]

An example of local spasm is shown in Figure 6. This patient had an aneurysm of the anterior communicating artery with episodes of subarachnoid bleeding two weeks and one day prior to angiography. The angiogram reveals a marked narrowing of the pericallosal artery, which might mistakenly be passed as showing no evidence of spasm. This type of local spasm should aid in indicating the location of a ruptured aneurysm.

In Figure 7 angiograms are shown of a patient whose aneurysm failed to fill on initial angiography in the presence of marked spasm. Three weeks later, after disappearance of the spasm, the anterior communicating aneurysm filled readily.

Spasm in this study was demonstrated on serial arteriograms with the finding of the same degree of contraction on different films of the same series, as well as on film series taken at varying intervals afterward. It was found to occur regardless of the contrast material used (iodopyracet [Diodrast], acetrizoate [Urokon], diatrizoate [Hypaque], colloidal suspension of thorium dioxide [Thorotrast]). In one instance, angiograms were repeated using another contrast agent (Thorotrast), but arterial constriction of the same degree was found.

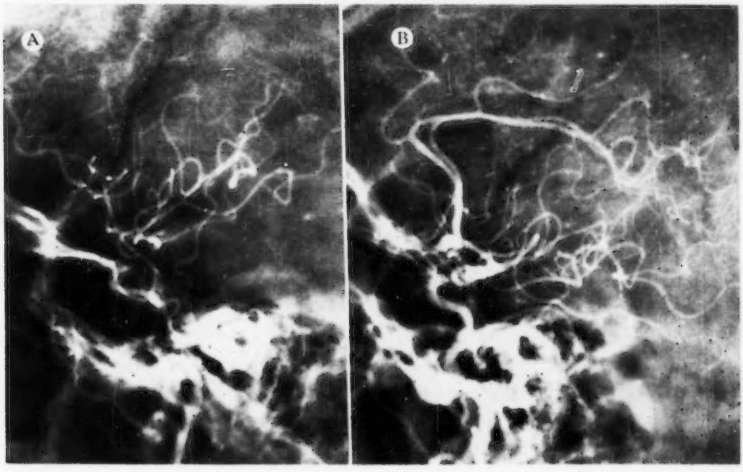
Comment

The mechanism of production and maintenance of arterial spasm in patients with

Fig. 7.—Failure to demonstrate aneurysm, which did not fill on initial angiogram, probably due to marked spasm.

A, 20 days following spontaneous subarachnoid hemorrhage from an aneurysm of the anterior communicating artery. There is marked spasm involving the internal carotid artery (supraclinoid region) and the anterior and middle cerebral arteries; however, the aneurysm does not fill. Note the faint visualization of the anterior cerebral artery. Bilateral angiograms were performed.

B, 21 days later, showing the aneurysm filled and vessels of normal caliber, after disappearance of the spasm (same case as that in Figure 2).



ruptured intracranial aneurysm remains a point for conjecture, but it appears primarily to be incident to local irritation at the site of rupture, since the association of spasm with gross subarachnoid hemorrhage was the most commonly noted feature in our series. It is also important to note that arterial spasm is rarely seen in conditions other than recently ruptured intracranial aneurysms. This suggests that subarachnoid bleeding alone may not be the only factor causing spasm but that local trauma or intra-arterial pressure changes may also play a role; that is, there may be a mechanical, as well as an irritative, factor.

Many surgeons have observed variations in caliber of cerebral arteries upon manipulation or dissection at operation, particularly about the circle of Willis, where the major basal arteries may react to mechanical stimuli by prompt local vasoconstriction.[16,17]

Recent hemorrhage about an aneurysm or traction on arterial walls resulting from its rupture or enlargement may result in a state of local hyperirritability of the musculature or intrinsic nervous control, which may then spread to distal segments.[16] In this series spasm was noted to occur after recurrent bleeding episodes in nine patients, although it was not demonstrated after the initial bleeding in some of these.

The usual immediate response to rupture of an intracranial aneurysm is for the vessels in continuity with the aneurysm and for a varying distance around it to go into spasm. While the occurrence of spasm may be delayed several days after the bleeding episode, it usually seems to occur within the first 10 days.

The result of such arterial constriction is to slow up, or possibly arrest, blood flow through the aneurysm sac. It also results in cerebral ischemia in the involved arterial territory; the severity of symptoms may be dependent upon the extent and duration of the spasm. Although recovery may be complete, permanent neurological damage may persist despite disappearance of the spasm. Hemiplegia, coma, aphasia, and other signs of neurological deficit may result from this functional impairment of circulation, as well as from the more commonly accepted causes of cerebral damage in these patients.[7,18] Relaxation of the arterial spasm appears to be a gradual process, occurring over a period of hours or days.

The treatment of ruptured intracranial aneurysm remains a difficult problem, but recent advances in surgical technique and their applications are giving heartening results. It seems probable that clip obliteration of a recently ruptured aneurysm may remove a source of local irritation serving to maintain a state of vasospasm in the adjacent arteries. In many cases, therefore, the complications of vascular spasm may be prevented or lessened by early operation and intracranial clip obliteration of the sac.

Summary and Conclusions

Cerebral vasospasm may affect the major arteries of the brain.

Spasm of one or more major cerebral arteries or their branches contiguous to an aneurysm is frequent after rupture of an intracranial aneurysm.

The clinical course and incidence of neurological signs may be related to the extent and duration of such spasm.

Vasospasm did not occur in major cerebral arteries having clear-cut evidence of arteriosclerotic changes, presumably because such vessels are no longer capable of spasm.

The type of vasospasm under discussion usually occurs within three weeks of aneurysmal rupture and is usually associated with bloody cerebrospinal fluid.

Recognition of the presence of vasospasm is of particular value as a guide to prognosis and management, and occasionally is of localizing value when an aneurysm fails to fill with contrast material or when multiple aneurysms are present.

The presence of gross blood as a local irritant is one explanation for the production of spasm. However, since spasm may occur in the absence of blood, and is usu-

ally absent on the opposite side from a bleeding aneurysm, there may be an additional factor in the production and maintenance of cerebral vasospasm. This could be a local muscle or nerve reflex effect caused by the distention or rupture of the aneurysm.

The occurrence of vasospasm and serious resultant neurological signs may be delayed for several days after subarachnoid hemorrhage, indicating consideration of prompt surgical treatment of ruptured intracranial aneurysms.

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Rathke-Cleft Cysts

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Rathke-cleft cysts are rare. For this reason alone, examples of this condition require recording. In addition, they are significant for the light which they may throw upon other tumors arising in the pituitary region, notably the craniopharyngiomas.

The reported incidence of residual cysts in the pars intermedia is 15% to 20% (Shanklin [28]). Most of these are microscopic in size and have greater histological than clinical significance. Occasionally, such cysts enlarge sufficiently to be seen on sectioning the hypophysis, but still lack clinical significance. Under rare circumstances a cyst enlarges sufficiently to cause clinical symptoms. Ten such instances have been recorded. To these is added another instance of Rathke-cleft cyst with clinical symptoms, as well as a similar large cyst found incidentally at autopsy.

Report of a Case

CASE 1.—A 49-year-old white woman was admitted to Jefferson Medical College Hospital because of progressive difficulty with vision and dizziness. She was a seamstress by trade and had encountered difficulty in seeing the finer details of her work for a period of one year prior to admission. A progressive loss of vision of the left eye became noticeable eight months before admission, followed in three and a half months by a left temporal visual field defect and drooping of the left eyelid. Two weeks later she complained of diplopia, which persisted for several weeks. At the age of 36 she underwent a hysterectomy for menorrhagia, due to fibroids. Three years later a thyroidectomy was performed because of a goiter. For a period of a year or two, prior to her present admission, she had noted loss of libido.

Physical Examination.—Upon admission, the physical examination was within normal limits. The vital signs were normal, with the blood pressure 115/75. She was described as pale and obese, but with normal fat distribution. Her skin was normal, and her hair was normal in texture and in distribution. No evidence, by inspection or palpation, of a pharyngeal hypophysis could be detected.

Neurological Examination.—Normal, except for the visual fields. A temporal field defect was present on the left side, involving central vision, with a less marked temporal field defect on the right side (Fig. 1).

Laboratory Data.—Hemogram and urinalysis were normal. Blood chemistry determinations, per-

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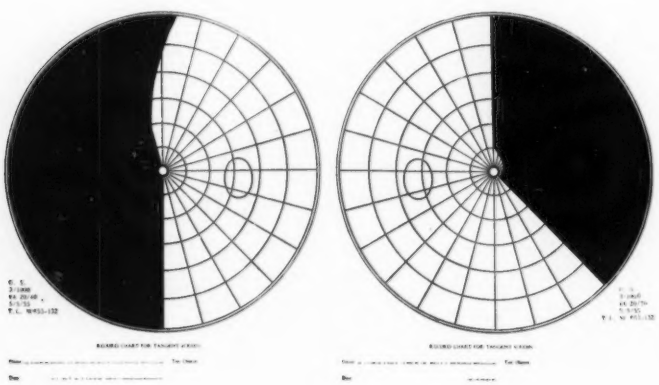

Fig 1 (Case 1).—Central visual fields prior to first operation. Uncorrected visual acuity in left eye 20/40, in right eye 20/70.

formed before surgery were as follows: BUN, 11 mg. %; fasting blood sugar, 85%; serum cholesterol, 285 mg. %; sodium, 137.5 mEq. per liter; potassium, 5.1 mEq. per liter; calcium, 10 mg. %; phosphorus, 3.25 mg. %, and alkaline phosphatase, 5.93 Bodansky units. The cerebrospinal fluid was under a pressure of 180 mm. of fluid; it was clear and colorless, with a protein content of 31 mg. %, a negative Wassermann reaction, and a colloidal gold curve of 0000000000.

Preoperative endocrine studies produced the following data: protein-bound iodine 5.25μg. %; I^{131} uptake 53%; basal metabolic rate —31%; 17-ketosteroids 5.2 mg. per 24 hours; urinary gonadotropins less than 6 mouse units; estrogens 24 mouse units. Intravenous glucose tolerance test (six-hour) was normal; insulin tolerance test showed resistance, with a flat curve.

An electroencephalogram was normal. The skull x-rays were reported as negative. Pneumoencephalography was performed, and, aside from the lack of filling of the cisterna lamina terminalis, the air studies were considered to be normal.

Course.—A preoperative diagnosis of hypophyseal adenoma was made, and the patient underwent surgery on May 16, 1955. The neurosurgeon, Dr. William H. Whiteley, described "a cyst protruding upward in front of the optic chiasm, stretching laterally the optic nerves. The cyst wall was transparent, and within the cyst was a clear, colorless, somewhat mucoid fluid. The entire pituitary fossa was explored, and no evidence of pituitary gland or tumor was found. The cyst occupied the entire sella turcica." A fragment of the cyst wall was removed for histological examination.

The patient survived the procedure well and remained asymptomatic for the succeeding two and one-half years. On reexamination, in February, 1956, and September, 1957, the only abnormality noted was a residual visual field defect (Fig. 2). Thorough endocrine evaluation failed to reveal any significant abnormalities.

On June 24, 1958, the patient was readmitted because of progressive loss in vision, in the right eye especially, during the previous several weeks. This visual loss suddenly became worse nine days prior to admission, with light perception only in the right eye. She complained of easy fatigability, constipation, and decrease in body hair, present since her previous surgery.

The significant findings were limited to the neurological status. There was complete blindness in the right eye and temporal hemianopsia in the left. There was bilateral optic atrophy, more pronounced on the right. Visual acuity in the left eye was 6/60, correctible to 6/12.

On June 27, a frontal craniotomy was performed by Dr. William H. Whiteley. A massive transparent cyst, about 3 cm. in diameter, was seen arising from the sella. It compressed the optic nerves and chiasm and extended about 1 cm. above the optic nerves. The thin-walled cyst contained a large amount of thin, homogeneous mucus. It was about three times the size of the previous cyst.

The postoperative course was satisfactory. Two months after surgery visual acuity in the left eye was 20/70, correctible to 20/40. There was no vision in the right eye. The visual field on the left showed a temporal hemianopsia.

Pathology.—The specimen obtained at the first operation, in May, 1955, was a small fragment of whitish tissue, having the appearance of thickened arachnoid. Histologically, the cyst wall showed a stroma of vessels and fibrous connective tissue with cords of cells, which tended to be arranged in parallel rows (Fig. 3). When cut in cross section, the cell rows had an acinar appearance. The stroma was reminiscent of the capsule of the pituitary and its pars tuberalis. In general, the cytoplasm of the

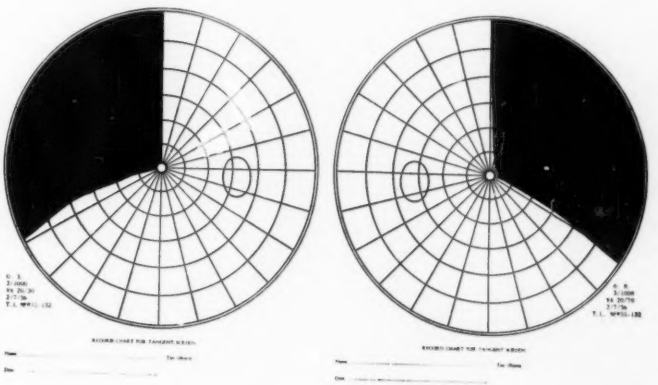

Fig. 2. (Case 1).—Central visual fields after evacuation of the suprasellar Rathke-cleft cyst. There is partial resolution of the left hemianopsia with little change in the right field.

Fig. 3 (Case 1).—Low-power view of cyst lining with columnar epithelium on right, connective tissue stroma on left.

Fig. 4 (Case 1).—Detail of a portion of the lining of a Rathke-cleft cyst.

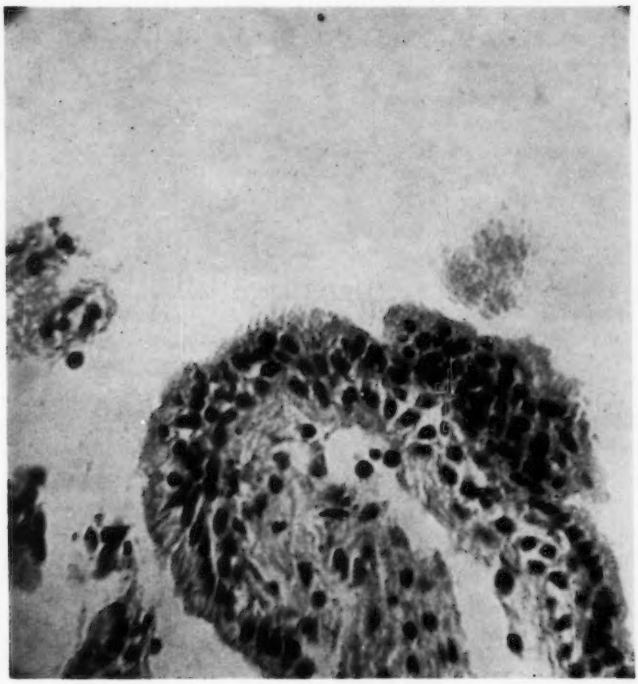

Fig. 5 (Case 1).—Lining of Rathke-cleft cyst cut tangentially suggests squamous epithelium in parts. A pseudociliated effect is presented by strands of mucinous material at the summit of many cells.

cells was vesicular; the cell nuclei were small, round, and dark. No specific granules were present.

Of greatest interest were fragments of pseudostratified columnar epithelium resting on a thin connective tissue core, in which were vascular sinusoids. The appearance of this columnar epithelium varied to some extent from place to place. In general, there were tall cells with oval nuclei at their base, and a more or less definite cytoplasmic border between the cells (Fig. 4). The cytoplasm was finely granular; occasionally it was vesicular with a bluish tinge, with a staining reaction for mucin. Other cells appeared compressed, with darker elliptical nuclei lying parallel to the stroma. There was a bubbling effervescence, presumably as an artifact of sectioning, on the summit of certain groups of cells, with strings of PAS-positive material, giving a pseudociliated appearance (Fig. 5). True cilia were not identified.

Some portions of this epithelium were composed of a low columnar type of cell, often resting on a basement layer of polygonal cells with scanty cytoplasm and round to oval nuclei. One or two areas superficially suggesting stratified squamous epithelium resulted from tangential sectioning.

Except for their lack of definite cilia, the epithelial cells were identical with those reported in other cases of Rathke-cleft cysts.

The specimen from the second operation was similar to that previously seen, with the exception of an increased thickening of the cyst wall with collagenous tissue stroma, within which were scattered inflammatory cells. There was no unequivocal squamous epithelium, but some areas had the appearance of squamous cells, apparently because of the angle of section. PAS-positive material was abundant in the epithelial cells.

The second hypophysis with a macroscopic cyst of Rathke's cleft was found in routine autopsy. Although a suspicion of panhypopituitarism was entertained clinically in this case, insufficient evaluation was obtained during the hospital stay to warrant such a diagnosis. No parapituitary symptoms were identified, and the case must be considered one of a macroscopic cyst incidentally found at autopsy.

Case 2.—A 60-year-old white woman was admitted to the hospital for the investigation of "black-out spells." There was a history of attacks of lightheadedness and dizziness of some 30 years' duration. These episodes were only rarely accompanied by actual fainting, until two weeks prior to admission.

Physical Examination.—The patient was obese and had pale, dry skin. Her hair was dry; the pubic hair was sparse, and no axillary hair was present. The blood pressure was 164/100 in the supine position and 130/90 in the upright. No other abnormalities were found on the general physical examination, and the neurological examination revealed nothing abnormal.

There was clinical and laboratory evidence of hypothyroidism. She died during an episode of hypotension, before full endocrine evaluation could be completed.

Autopsy showed generalized arteriosclerosis with occlusion of the left common carotid artery by arteriosclerotic plaques. The thyroid gland was atrophic, with a small nodule in the right lobe. The brain showed evidence of a relatively recent infarct in the left cerebral hemisphere in the distribution of the middle cerebral artery.

The hypophysis was enlarged, measuring 16×13×6 mm. in the fixed state and weighing 1.12 gm. On sagittal section, a pearly white, oval cyst, measuring 7×5 mm., was found replacing most of the posterior lobe, and a suggestion of fibrous degeneration of the anterior lobe was present (Fig. 6).

On histological examination, the hypophyseal cyst was seen to be lined with ciliated columnar epithelium, with occasional goblet cells containing mucin (Fig. 7). Most of the contents of the cyst disappeared in fixation, but the remnants consisted of a mucinous material and some cellular debris.

Fig. 6 (Case 2).—Colloid cyst in hypophysis.

Comment

In the majority of instances, Rathke-cleft cyst is an incidental finding at autopsy. In rare cases it may produce clinical symptoms. Goldzieher [13] reported a case of diabetes insipidus with a large colloid cyst of the hypophysis found at autopsy. In Duffy's [7] Case 4 a large adenoma of the hypophysis was present, but there was also an incidental cyst of Rathke's cleft, lined with ciliated columnar epithelium and with small tubular glands within its wall. Kiyono [16] described

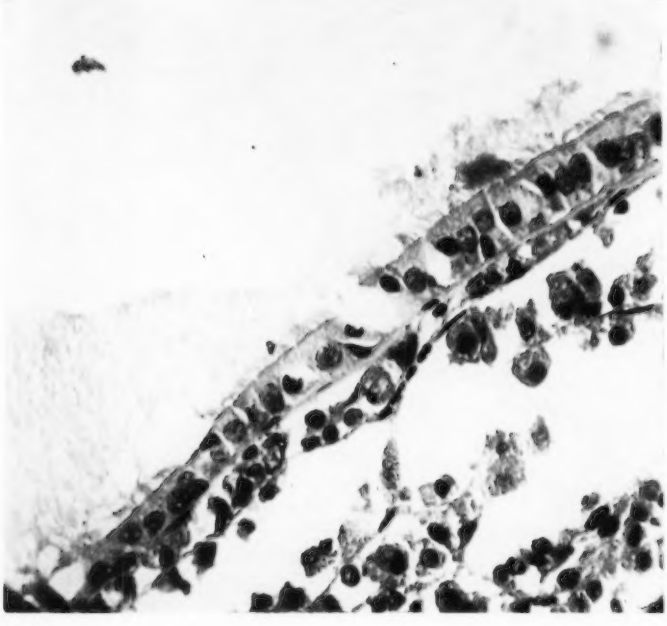

Fig. 7 (Case 2).—Ciliated columnar lining of colloid cyst seen grossly in Figure 6. Much of the contents of the cyst was lost in fixation. Scattered goblet cells contained mucin.

a case of hypophyseal cachexia due to a colloid cyst which was lined with ciliated epithelium. A Lorain type of hypopituitarism in a 17-year-old girl was recorded by Worster-Drought and associates.[30] At autopsy, a fragment only of anterior and posterior lobe tissue was found, compressed by a cystic tumor lined with ciliated epithelium. Fulstow[11] described an intrasellar cyst which she called a dermoid, but which was lined with "stratified squamous epithelium with long papillary projections. On some portions of the surfaces of the papillary projections, rather low ciliated columnar epithelium was seen, and in some similar locations there were epithelial cells containing globules of mucoid secretion, like those found in the epithelium of secreting glands." Frazier and Alpers[10] described a biopsied cyst which was lined with ciliated epithelium. Baar[1] reported two cases of pituitary cachexia in childhood, both associated with large colloid cysts of Rathke's cleft, with pressure atrophy of the anterior hypophysis. A Rathke-cleft cyst with clinical features of a chromophobe adenoma was described by Bayoumi.[2] Schermann and Barretto Netto[25] found complete destruction of the hypophysis by a cyst lined with ciliated columnar epithelium in a patient with no hypophyseal symptoms. The case recorded by Smith and Bucy[29] gave rise to symptoms suggesting a chromophobe adenoma. A brief description of four cases, in a personal communication from Dorothy Russell[24] to them, is contained in their paper, but no information is given as to clinical symptoms. A surgical specimen described by Messimy, Namin, and Martinès[19] was removed from a patient with symptoms suggesting a pituitary adenoma.

The reported cases fall into three clinical groups: (1) cases with predominantly suprasellar symptoms; (2) cases with pictures of hypophyseal dysfunction, and (3) cases with no symptoms referable to the hypophysis or hypophyseal region.

In the first group, in which suprasellar symptoms were paramount (Table 1), the usual preoperative impression was that of chromophobe adenoma of the hypophysis. All, save Bayoumi's[2] case of a 14½-year-

TABLE 1.—*Cases of Rathke-Cleft Cyst with Suprasellar Symptoms*

Author	Age, Yr.	Sex	Symptoms	Pathology
Bayoumi [2]	14½	F	Visual disturbance, 2 yr.; weight gain; diabetes insipidus; bilateral optic atrophy X-ray sella: "open and flat"	* Suprasellar cyst; columnar epithelium (with mucous and immature epidermoid cells); no cilia; calcification and osteoid tissue in wall
Berry & Schlezinger Case 1	48	F	Progressive visual symptoms, 8 mo., dizziness; bitemporal hemianopsia; decreased libido; early optic atrophy X-ray sella: negative	* Supra- and intrasellar cyst; columnar epithelium with mucous cells; no cilia; no colloid; no calcification
Frazier & Alpers [10]	52	M	Headache, 2 yr., progressive visual difficulties; blind OD; temporal defect OS X-ray sella: negative	* Supra- and intrasellar cyst; ciliated columnar to squamous epithelium; no mucin or colloid; no cholesterol; no calcification
Fulstow [11]	48	M.	Headache, 8 mo., disturbed heat regulation; diabetes insipidus; impotence X-ray sella: negative	† Supra- and intrasellar cyst; ciliated columnar and stratified squamous epithelium; mucoid secretion; cholesterol and foreign-body giant cells; no calcification; colloid cysts in wall; hypophysis compressed
Messimy, Namin, & Martines [19]	58	F	Progressive visual symptoms, 6 yr.; headache; bitemporal hemianopsia X-ray sella: enlarged	* Suprasellar cyst; cuboidal or columnar epithelium with cilia; colloid-filled acini; no mucin
Smith & Bucy [29]	41	M	Visual difficulties, 13 mo.; sup. rt. temp. field defects; pale discs; BMR 37%; decreased libido; no response to x-ray therapy X-ray sella: enlarged	* Intra- and suprasellar cyst; columnar to cuboidal epithelium; no cilia

* Biopsy material.
† Autopsy material.

old girl, occurred in the fifth or sixth decade of life, and no apparent sex difference was present. Since in all but one case the tissue was a biopsy specimen, only fragments of the cyst wall presumably were available. The duration of clinical symptoms varied from eight months to six years, but averaged about two years prior to operation. The usual history was that of progressive visual loss, due to pressure on the optic chiasm. Headache was prominent in three of the six cases. Hypothalamic-hypophyseal symptoms were present in most cases, but often occurred relatively late in the clinical course. The physical findings were limited to visual field defects in the temporal quadrants, with varying degrees of optic atrophy. The sella turcica was usually normal as seen by x-rays, but sometimes it was enlarged. Suprasellar calcification was not present on x-ray examination.

Microscopically, the biopsy fragments revealed connective tissue stroma, with cells containing few, if any, specific granules. The characteristic morphologic structure consisted of cuboidal to columnar epithelial cells with or without cilia and usually showing some transition to mucin-secreting goblet cells.

Few data are available concerning prognosis, although Smith and Bucy [29] inferred from the literature that the course was relatively benign as compared with that of an hypophyseal adenoma or craniopharyngioma. In the present report, Case 1 has been followed for over three years. It is evident that the recurrence of an incompletely removed cyst carries with it a serious threat to vision. Radiation therapy was of no help in Smith and Bucy's case, and surgery appears to be the treatment of choice.

That group of cases in which the presenting picture was hypophyseal dysfunction is shown as Table 2.

The compression of the posterior lobe with symptoms of diabetes insipidus, as in Goldzieher's [13] case, and of the adenohypophysis in the other cases is strong evidence that the hypopituitarism was related to the cyst. In general, the patients in this second group were younger than in either of the other groups. The patients ranged from 4 to 34 years of age. All specimens were obtained post mortem. In each case there was clinical evidence of decreased hypophyseal function, often of a severe nature.

The cysts were mainly intrasellar, accounting for the characteristic picture of a large cyst compressing the hypophyseal structure, and thus for the clinical symptoms. The cyst was lined by cuboidal epithelium, in some instances ciliated. In one case reported by Worster-Drought et al.[30] an associated suprasellar neoplastic transformation of the intrasellar contents was found. In Baar's [1] second case an associated dilatation of the residual lumen of Rathke's cleft was present. Each of these Group II cases

TABLE 2.—*Cases of Rathke-Cleft Cyst with Hypopituitary Symptoms*

Author	Age, Yr.	Sex	Symptoms	Pathology
Baar [1]				
Case 1	4	M	Hypophyseal cachexia	* Intrasellar colloid cyst, lined by flat to cuboidal cells; hypophysis compressed
Case 2	8	F	Hypophyseal cachexia	* Intrasellar colloid cyst, cuboidal epithelial lining; Rathke's cleft dilated; hypophysis compressed
Goldzieher [13]	34	M	Diabetes insipidus	* Colloid cyst; posterior lobe of hypophysis compressed
Kiyono [14]	28	M	Hypophyseal cachexia	* Colloid cyst; ciliated epithelial lining; hypophysis compressed
Worster-Drought, et al. [30]	17	F	Lorain-type hypophyseal infantilism	* Supra- and intrasellar cyst, lined with ciliated epithelium, with suprasellar "neoplastic transformation"; cholesterol in wall; hypophysis compressed

* Autopsy material.

TABLE 3.—*Cases of Rathke-Cleft Cyst Without Definite Symptoms*

Author	Age, Yr.	Sex	Symptoms	Pathology
Berry & Schlezinger Case 2	60	F	No definite hypophyseal symptoms (hypothyroidism)	* Intrasellar cyst; ciliated columnar epithelium; mucous cells; gland-like structures in wall; hypophysis compressed
Duffy [7] Case 4	--	--	Symptoms due to chromophobe adenoma	* Chromophobe adenoma; intrasellar cyst lined with ciliated columnar epithelium with goblet cells; gland-like structures in wall
Russell [24] Case 1	--	--	Unknown	* Suprasellar cyst lined with ciliated epithelium
Case 2	--	--	Unknown	* Intrasellar cyst lined with ciliated epithelium
Case 3	--	--	Unknown	* Dumbbell-shaped cyst; intrasellar portion lined with ciliated epithelium; suprasellar portion lined with squamous epithelium
Case 4	--	--	Unknown	* Dumbbell-shaped cyst; intracellar portion lined with ciliated epithelium; suprasellar portion lined with squamous epithelium
Schermann & Barretto Netto [25]	56	M	No hypophyseal or suprasellar symptoms	* Intrasellar cyst; ciliated columnar epithelium; hypophysis "completely destroyed"

* Autopsy material.

contained colloid within the lumen with no reported mucous cells, although in the photograph of Worster-Drought's case goblet cells are present.

The third group (Table 3) is a heterogeneous collection, of interest from the clinical standpoint because symptoms were lacking despite the size of the cyst. They are of further interest from the pathological viewpoint because of the possible relationship of simple "colloid cysts," mucus-containing cysts, and the squamous epithelial suprasellar cysts which are included with the craniopharyngiomas.

From this compilation of the literature no distinguishing clinical features serve to differentiate preoperatively between Rathke-cleft cysts and other suprasellar lesions, particularly craniopharyngiomas or chromophobe adenomas which have extended through the dorsum. Such a cyst must be considered as a rare cause of the chiasmal syndrome, or of hypopituitarism in a child or young adult.

Pathogenesis

Duffy [7] described two groups of tumors of hypophyseal-duct origin: The squamous epithelial-cell tumors and the cysts arising from Rathke's cleft. The squamous-cell tumors (craniopharyngiomas) were further subdivided into (1) intracystic papillomas (benign simple papillary cysts); (2) simple and more complete adamantinomas, the more complicated simulating teratomas (benign or locally malignant), and (3) the rare "spinal-cell" carcinomas.

Critchley and Ironside [6] emphasized the transition between Duffy's squamous-cell tumors Types 1, 2, and 3. Frazier and Alpers [10] followed Duffy's classification and further stressed the separation of the craniopharyngioma group of tumors (the so-called Rathke-pouch tumor, or tumor of the hypophyseal duct) from the Rathke-cleft cysts. In addition, Frazier and Alpers found an area of squamous epithelium in the wall of their reported case, hinting at a possible connection between the two types of tumors. They expressed some concern over the origin of the ciliated cells in their Rathke-cleft cyst.

Studies of the anatomy and development of the hypophysis, such as those of Shanklin [27,28] and Bayoumi,[2] cast some light on the origin of these Rathke-cleft cysts.

Rathke's pouch, being the dorsal outpocketing of the stomodeum, is lined by epithelial cells of ectodermal origin arising from the buccal cavity. At about the 21 mm. stage of the embryo, the neck of the pouch at the buccal-pharyngeal junction becomes occluded. A small *Rathke's cleft* remains. The glandular portion of the hypophysis develops from these remnants of buccal epithelium. But residual Rathke-cleft cells remain in the pars intermedia.

In the normal course of events, during early life gland-like structures are present in the posterior lobe which connect by ducts with the cleft lumen. With age, these *tubuloracemose glands* involute and are present only rarely as independent structures in the adult.[17] Their only residua are the "salivary" glands of Erdheim,[8] and probably the basophil-like cells of the proximal part of the posterior lobe. At the same time, the lumen of Rathke's cleft collapses and in its process of involution breaks up into a variable number of small cysts, often distended with colloid.

The epithelium of these cystic residua reflects the variable potentials of the embryonic epithelium in the normal process of differentiation and development.[20] The buccal epithelium is capable of differentiating into ciliated columnar epithelium of Rathke's cleft [2,12,22,28] and into the chromophobe-chromophil cells of the pars anterior of the hypophysis.[5,15] With involution of Rathke's cleft, the ciliated epithelium changes to mucus- or colloid-secreting epithelium, which may be cuboidal or flat, or, rarely, into squamous epithelium.[21,23,26,28] These different types of cells have been described intermingled in the cyst wall with granular cells of the pars anterior.

Hypophyseal cysts have been described by Shanklin in four categories [28]: 1. Cystic dilatations of Rathke's cleft. The collapsed cleft of the adult is lined with epithelial cells, and either it has no lumen or its place is taken by multiple small cysts containing colloid and lined with cuboidal to flattened epithelium. These microcysts are present in the pars intermedia and often extend into the posterior lobe of the hypophysis. They appear to be residuals of the cleft lumen, as though pinched off in the process of closure. 2. Microfollicular cysts derived from the tubuloracemose glands. There is a likelihood that these gland-like structures may become pinched off but continue secreting, thus forming follicular cysts, similar to retention cysts elsewhere in the body.[8,28] 3. Hypophyseal-stalk cysts. 4. Cysts resulting from degeneration of adenomas or following infarcts of the hypophysis.

Not only do the tubuloracemose glands seem to be actively secretory but the residual cleft lining appears to secrete colloid. There must be a balanced secretory and absorptive phase in the working of these glands, or more macrocysts would be demonstrable.[27] The cysts and the cleft contain not only colloid but cellular debris and mucicarmine-positive material from the goblet cells in the walls of the cyst.

Serial sections have demonstrated ciliated cells in at least some areas of all residual lumina.[2,28] These ciliated cells occur at all ages and in the entire vertebrate kingdom. It may be from mechanical pressure that cilia are lost in many specimens, or it may be in the natural transition from ciliated to cuboidal or mucus-secreting cells that the cilia disappear. Be that as it may, it should cause no undue concern that several Rathke-cleft cysts have been described without cilia in those portions available for histological study.

In anatomical specimens, the development of squamous epithelium has been less frequently noted, but evidence of this endpoint in the genesis of epithelium is not lacking.[18,21,23] Squamous epithelium is more frequently noted in the pathological cysts in the literature. In Dorothy Russell's [24] specimens, ciliated epithelium lined the cysts except in the suprasellar portion of the dumbbell-shaped cysts, which were lined with squamous epithelium. In Fulstow's case [11] the cyst was lined with stratified squamous epithelium with some ciliated

columnar epithelial areas, as well as goblet cells containing mucus. Frazier and Alpers [10] noted areas of squamous epithelium and considered it possible that a transition occurs between these two types of epithelium: the ciliated and the squamous.

There are, in the region of the pituitary and sella turcica, a number of cysts and tumors which may bear a relationship to one another; of these, the true Rathke-cleft cysts may serve as the basic type, the others representing developments from the remnants of Rathke's cleft. Efforts have been made to indicate that remnants of transitional epithelium between the simple cell lining of Rathke's cleft and the epithelium of the buccal ectoderm may give rise to the craniopharyngiomas (Frazier and Alpers [10]).

Cysts of Rathke's cleft have been reported with cuboidal cells, columnar cells, and modified squamous epithelium. Cilia have been observed in some instances, but not in all.

The distinction between a true Rathke-cleft cyst and a craniopharyngioma depends not exclusively on the presence of cilia. More significant is the nature of the cell lining the cyst. While this has not been uniform in the examples which have been reported, the crucial observation lies in the fact that the cell type differs greatly from the epithelial structure of the craniopharyngioma. In the Rathke-cleft cyst, there are flat, cuboidal, or columnar cells, with or without cilia; but, except in transitional areas, the squamous epithelial cell found in the craniopharyngiomas is lacking.

The cysts which have been described as Rathke-cleft cysts probably represent a true remnant of Rathke's cleft. They are histologically distinct from the craniopharyngiomas and from other epithelial tumors in the hypophyseal region. No conclusive evidence has been found to indicate that the craniopharyngiomas may represent an outgrowth of the Rathke-cleft cysts, though in a few instances transitional epithelium has been found from the flat, cuboidal, or columnar cells lining the Rathke-cleft cyst.

Summary

Two examples of Rathke-cleft cyst are described. One resulted in a chiasmal syndrome, and the other was found incidentally at autopsy.

The histopathology and probable development of these rare cysts are briefly described and contrasted with that of the Rathke-pouch tumor (craniopharyngioma).

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P^{32} Uptake by Normal and Ultrasonically Irradiated Brain Tissue from Cerebrospinal Fluid

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There is evidence that the blood-brain barrier concept holds true not only for large molecules but for a great number of ions. Radioactive isotopes are not completely prevented from entering the internal environment of the central nervous system, but their passage from plasma to brain substance is reduced and delayed. However, the exchange of the same isotopes between plasma and cerebral lesions caused by trauma, irradiation, inflammation, vascular disorders, or neoplasms is more or less free. Consequently, a high concentration of radioactivity can be observed in lesions compared with surrounding normal brain tissue.

Explanations of these phenomena can be arranged in two main groups. One theory lays emphasis on the increase of local capillary permeability, while the other identifies the selective barrier function with the function of cerebral tissue proper. When applied to pathological observations, this second theory would imply that metabolic rather than vascular changes within the lesion are responsible for the increased isotope concentration.

In the experiments described below, P^{32} was brought in contact with normal and injured brain directly or by using the cerebrospinal fluid as an intermediary. We assumed that by circumventing the blood-brain barrier and by excluding the vascular channels important data could be obtained regarding the tissue aspect of ion exchange. The lesion should concentrate more P^{32} than normal cerebral tissue, whatever the route of its access to the isotope, if such selective uptake is based on tissue affinity and cellular requirement alone.

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Material and Methods

The experiments were performed in 12 cats. Lesions were produced by focused ultrasound. The ultrasonic irradiation technique was described in detail in a previous communication (Bakay, Hueter, Ballantine, and Sosa [4]). It consisted of pulsed irradiation by means of an ultrasonic applicator made up of a piezoelectric quartz plate and a polystyrene lens coordinated with the Horsley-Clark apparatus. Application of ultrasonic radiation made the production of lesions of predetermined size possible without any damage to the tissue lying between lesion and cerebral surface.

In the first group of experiments P^{32} was injected into the cisterna magna. In five of the cats a lesion was produced in the area of the lateral geniculate body in close proximity to the ambient cistern. Focused ultrasound of 2.5 megacycles and a focal intensity of 500 to 1,700 watts per square centimeter was applied. The resulting lesions were spherical or slightly oblong and varied from 3 to 5 mm. in diameter. In three cats small lesions were produced on the surface of the parietal cortex or underneath it in order to study the P^{32} exchange between these tissues and the subarachnoid CSF. After ultrasonic irradiation, 3 to 5 cc. of a 1% trypan blue solution was injected intravenously to outline the area of damage, because small ultrasonic lesions are frequently invisible to the naked eye in the gross specimen unless they are vitally stained. Afterward an isotonic solution of $NaH_2P^{32}O_4$ was injected into the cisterna magna at one hour to three days following the ultrasonic irradiation. Cisternal fluid in the amount of 0.4 to 0.8 cc. was slowly removed and replaced with 0.3 to 0.7 cc. of P^{32} solution containing 3μc. to 15μc. of the isotope. Chemical determination revealed that the

amount of inorganic phosphorus did not exceed 1.9 mg. % in the solution. This is within normal range for CSF phosphorus, and, therefore, the danger of establishing an abnormal chemical concentration gradient for phosphate between cerebrospinal fluid and brain was avoided. The cats were killed from 10 minutes to 8 hours after the cisternal injection. At the time of death CSF was taken from the cistern and blood from the heart. The brain was immediately removed and frozen. Sections of 0.3 to 0.5 mm. thickness were used for contact radioautography. Direct determination of radioactivity was done in dried samples of brain, plasma, and cerebrospinal fluid by end-window Geiger-Müller counters.

In the second group, of experiments (four animals), P^{32} solution was applied directly to the cortex. Relatively small spherical lesions (0.8 to 1.5 mm. in diameter) were produced in the lower cortical lamina and in the subcortical white matter of the marginal gyrus of the parietal lobe near the midline. The lesions were separated from the surface by the uninjured upper layers of the cortex. From 35 to 140 minutes following the lesion making, the dura was removed from the exposed portion of the irradiated, as well as of the contralateral, parietal lobe. The sagittal sinus was preserved. Hartmann solution, in the amount of 1.5 to 2.0 cc., was then applied over the exposed cortex. Mixed into this solution was 0.2 to 0.3 cc. of a P^{32} solution containing 15μc. to 30μc. of the isotope. Actually, the solution during these experiments was placed subdurally rather than subarachnoidally, but experience showed that it nevertheless diffused into the brain substance through the pia-arachnoid after a slight initial delay. Removal of the leptomeninx was not feasible because it invariably resulted in trauma to the cortex. After 55 to 200 minutes of application, the solution was carefully removed from the cortex, and the cats were killed. Cisternal fluid and heart blood were taken, and the brain was removed and frozen after a rapid perfusion of both carotid arteries with saline and 10% formalin to facilitate the subsequent sectioning of the brain. Previous work [8] has shown that such perfusion does not significantly interfere with P^{32} recovery in the central nervous system, even when the tracer is injected intravenously. Frozen sections of 50μ to 100μ thickness were made serially through the lesion and the corresponding normal hemisphere and used for contact radioautography. Alternate sections were stained histologically. The radioautographs were developed in groups of two, following gradually increasing exposure time, so as to be able to observe the step-by-step diffusion of P^{32} into the various layers of the cortex and through the lesion.

Results

1. *Cisternal Injections.*—The inorganic phosphate content of the cerebrospinal fluid varied from 0.8 to 2.2 mg. %. However, when a large ultrasonic lesion was produced in direct contact with the fluid of the ambient cistern, the inorganic phosphate content of the CSF increased to 4 mg. %. Under such circumstances the CSF is colored by trypan blue, presumably by diffusion from the lesion. Vital coloration of the CSF does not occur with lesions that do not present themselves on the ventricular surface. The increase of phosphate could have been caused by an increased permeability of the blood-CSF barrier. However, the close relationship between lesion and CSF, as well as the absence of any injury to the choroid plexus, suggests cerebral tissue breakdown as the cause of phosphate increase, a process that has been demonstrated in other lesions of the central nervous system.[7,11]

After its injection, P^{32} disappeared rapidly from the cisternal fluid. Twenty minutes later the cisternal CSF contained only 20% to 25% of the radioactivity of the injected solution, and this amount was reduced to 5% in two hours and to less than 1% in three hours. The rate of disappearance from the CSF was similar to that found in rabbits.[8] It is interesting that this rapid P^{32} exchange between CSF and surrounding tissues is very similar to the P^{32} exchange through the capillary walls between plasma and various organs of the body (but not the brain) following intravenous injection. This indicates that a large portion of the cisternally injected isotope, possibly two-thirds or three-fourths, is absorbed within a half-hour by the brain substance and by the venous circulation of the meninges.

The P^{32} concentration of the plasma remained low several hours after cisternal injection, although a significant amount of the isotope must have become absorbed by the blood stream. However, this was immediately diluted by the large volume of circulating plasma, and not more than a few counts per milligram per minute were re-

corded by the scalers. The plasma concentration was fairly steady during the first hour and showed no striking signs of decrease from isotope loss by transcapillary exchange. The compensatory mechanism against such loss must have been a steady feeding of the tracer into the blood stream by the cerebrospinal fluid. Fortunately, the constantly low plasma concentration caused by loss and dilution eliminated the danger of a secondary concentration of P^{32} in the cerebral lesion via the damaged blood-brain barrier.

Calculation of the total radioactivity revealed that 30 minutes following cisternal injection the CSF contained 20% of the injected P^{32} and the brain 20%. About 8% was circulating in the blood, and the rest was deposited in various organs, including intracranial but extracerebral structures. The radioactivity of the meninges and skull was high. The total amount of P^{32} outside the brain and CSF was, therefore, 60% of the injected amount. According to the calculations of Sacks and Culbreth [12] in cats in the course of four hours after the injection into the cisterna magna, about 60% of the tracer appeared to be absorbed into the general circulation, most of it during the first hour after the injection. The uptake by the brain was similar to that found in rabbits at 30 minutes by Bakay and Lindberg.[5] It also seems to be in good agreement with recent findings by Herlin,[8] who reported 56% of P^{32} in the brain, 26% in the skull, 18% in the rest of the body, and only a small fraction in the cerebrospinal fluid in rabbits one hour after intracisternal injection.

The tracer seemingly did not become evenly mixed in the CSF within the range of these experiments. The main pathways of flow lead from the cisterna magna to the pontine cisterns, and from there partly to the basal cisterns and partly to the convexity via the ambient cisterns and the interhemispheric cistern. In some experiments the two routes were of equal importance, but in others one prevailed considerably over the other. The CSF content of most of the cisterns and subarachnoid spaces was too small for analysis, but the pattern of isotope distribution was clearly seen on radioautographs. It could be relatively calculated by determining the P^{32} content in the most superficial layer of brain tissue adjacent to the CSF spaces (Table 1). In a typical experiment, gradually decreasing tracer concentration was found along the ambient cisterns and the interhemispheric cistern. The cortex bordering the posterior portion of the interhemispheric cistern sometimes contained 30% more P^{32} than that near the midportion, and 70% to 150% more than that of the anterior portion near the frontal pole, as late as two hours after cisternal injection. In other experiments of shorter duration the mixing was faster.

Activity diminished in the brain from surface to depth; this was revealed by direct tissue counting. Radioautographs also revealed this point, but only when a series of increasingly long exposure times was used. Lack of adequate reflux of P^{32} into the

TABLE 1.—*P^{32} Content of Various Parts of the Brain Following Cisternal Injection* *

Time elapsed	10 min.	21 min.	45 min.	2 hr.	3½ hr.
Amount of CSF removed, cc	0.8	0.5	0.5	0.8	0.8
Amount of solution injected, cc	0.7	0.4	0.3	0.6	0.6
Cisternal fluid		122-163	95	37	2.4
Plasma	2.9	0.7	2.5	0.5	0.5
Medulla	167	535	525	142	144
Surface of cerebellum	211	484	226	120	22
Wall of fourth ventricle	222	166	196	36	16
Lower midbrain, surface	70	284	346	60	32
Wall of ambient cistern	45	107	476	80	44
Wall of interhemispheric cistern	72	154	6	66	8
Wall of basal cistern	42	83	1,036	40	250

* Data are given in counts per milligram per minute and calculated to an intracisternal dose of P^{32} of 10 μc.

ventricular system prevented absorption of the isotope by deeper structures from the ventricular CSF. The isotope arrived promptly in the fourth ventricle, but further flow beyond the aqueduct was slight; and only a small amount of P^{32} was found in the walls of the third and lateral ventricles. The ambient cistern in those animals in which the lesion was placed next to it was considerably compressed by edema around the lesion and transmitted less P^{32} to the interhemispheric cistern than its mate on the normal side. This also might have interfered with free mixing of P^{32} through the aqueduct, although this latter structure never became anatomically obstructed. Probably the main reason for the lack of ventricular mixing was our practice of injecting a smaller amount of isotope solution into the cisterna magna than the amount of CSF removed. Increase of the cisternal pressure is a prerequisite to assure retrograde flow into the ventricular system, and we tried to avoid building up a local pressure head in the course of these experiments. Retrograde flow into the relatively large ventricular system of such lower mammals as rabbits contributes a great deal to the experimental isotope exchange between CSF and brain, because even the deepest layers of the thin neopallium are within diffusion range from the external and internal surfaces. Phylogenetic increase in the width of the pallium slows down the diffusion into deeper layers. The increase in the gyrus formation of the brain does not compensate for this because, at least in short-ranged experiments, the isotope solution does not get evenly mixed with whatever fluid there is in the depth of the sulci.

The lesions did not concentrate more P^{32} than the corresponding normal portions of the contralateral hemisphere, as seen in radioautographs (Fig. 1), although the tracer was readily available for incorporation, having reached the area of the lesion by diffusion from the nearest subarachnoid space. This behavior represents a marked contrast with the increased isotope concentration by the lesion following intravenous injection (Fig. 1). Direct determination of the P^{32} content of tissue showed that the lesion adjacent to one of the ambient cisterns contained only 40% of the P^{32} content of the corresponding region on the other side at 10 minutes after cisternal injection. This relationship did not change with time and was found to be 38% at 20 minutes and 15% at 2 hours. One could assume, therefore, that the lesion has not taken up more P^{32} from the CSF than its topographically corresponding normal counterpart. The fact that it actually took up less is of no

Fig. 1.—Upper: Cross section of cat's brain. Arrow points to an ultrasonic lesion adjacent to the ambient cistern, vitally stained with trypan blue 80 minutes after irradiation. Middle: Radioautograph of same section 10 minutes after cisternal injection of 9μc. of P^{32}. Exposure time, 74 hours. White areas correspond to high P^{32} concentration. The concentration of the isotope is not increased in the lesion (arrow). Lower: Radioautograph of cross section of cat's brain of the same thickness 110 minutes after intravenous injection of 500μc. of P^{32}. High concentration of P^{32} is seen in the ultrasonic lesion (arrow), which was produced one hour before the isotopic injection. Exposure time, 48 hours.

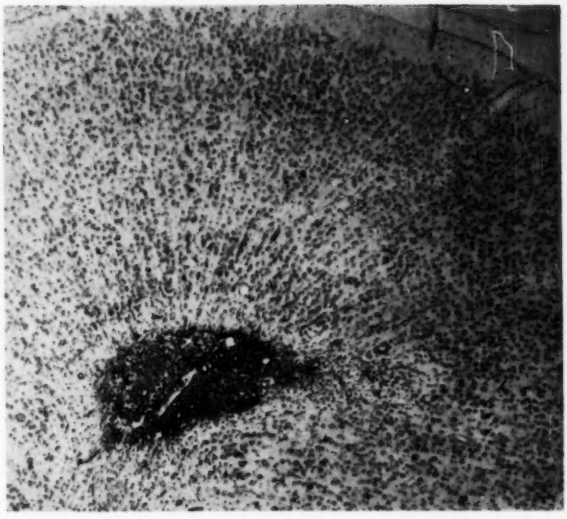


Fig. 2.—Microscopic picture of ultrasonic lesion at border of parietal cortex and white matter 72 hours after irradiation. Cresyl violet stain; × 60. Lesions such as these do not take up more P^{32} from the CSF than does normal brain tissue, despite vigorous macrophage activity.

significance, since a greater amount of the cisternally injected isotope circulated in the ambient cistern opposite to the lesion, owing to the local edema around the lesion. When correction was applied for this uneven distribution in the two ambient cisterns, the counts in lesion and normal midbrain became roughly equal. The total chemical phosphate content was determined in these relatively large lesions, and was found to be over 90% of the corresponding normal brain; consequently, the findings cannot be explained by a rapid phosphate loss of the irradiated tissue.

There was no significant swelling around small cortical and subcortical parietal lobe lesions, and in all but one of the experiments the P^{32} solution was evenly distributed in the subarachnoid spaces of both hemispheres. Both the lesion and its normal counterpart concentrated equal amounts of the isotope 23 minutes, 2 hours, and 8 hours following cisternal injection. There was no difference in uptake between acute and three-day-old lesions, although the latter showed dense cellularity in microscopic sections (Fig. 2). The only exception occurred in a three-hour experiment, where the entire cortex of the irradiated hemisphere, including the lesion proper, contained three times as much P^{32} as the contralateral lobe. However, even in this case the uneven distribution of P^{32} was nonspecific and not localized to the lesion itself.

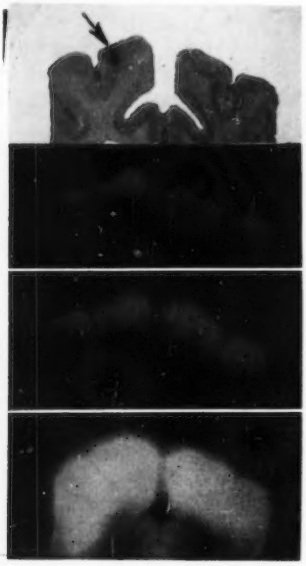
2. *Direct Cortical Application of P^{32}.*—It was thought that by applying the tracer solution directly over the exposed cortex, P^{32} exchange between brain tissue and overlying solution could be studied more directly without the complicating factor of uneven and unpredictable mixing of the tracer in the CSF that inevitably follows cisternal administration. The tracer solution diffused into the cortex but did not enter the general CSF circulation, since there was no significant CSF circulation underneath the arachnoid membrane of this isolated surface. The diffusion was limited to the cortex of the exposed area. The CSF collected from the cisterna magna at the time of death showed no radioactivity. On the other hand, absorption into the blood stream was observed. Some of this must have occurred through the cerebral capillaries of the diffused area, but the bulk probably became absorbed by the diploic veins, the sagittal sinus, and the exposed edge of the temporal muscle.

The radioactivity of the isotope solution was determined before and after its applica-

tion to the cerebral surface. It showed no change, even after three hours, and hence was not diluted by tissue fluid. The initial amount of the solution was compared with the final amount, and the fluid loss was compared in terms of total radioactivity with the amount recovered in the brain and blood plasma. This revealed that 55 minutes after its application over the cortex 31% of the P^{32} content absorbed was in the brain tissue, 30% in the circulating blood, and none in the cerebrospinal fluid. The remaining 39% was obviously taken up by other organs, some of it through the blood circulation and some directly by the tissues around the edge of the craniotomy.

The gradual diffusion of P^{32} into the cortex and subcortical white matter was followed by radioautography and direct tissue analysis. In none of the experiments was there any concentration of P^{32} in the lesion as compared with the surrounding or contralateral normal brain tissue (Figs. 3 and 4; Table 2). In one of the experiments the core of the lesion, which showed considerable tissue coagulation, contained little P^{32}. The other three experiments revealed no difference between the center of the lesion and the surrounding, equally trypan-blue-stained zone of reaction and comparable normal brain.

Fig. 3.—Upper: Unstained, dry-frozen section (100μ) of both upper parietal lobes of cat. Arrow points to vitally stained lesion, produced by ultrasound four hours before death. Below: Radioautograph of same section 200 minutes after application of a P^{32} solution over the pia-arachnoid-covered cortex. White areas correspond to the diffusion of the isotope into brain tissue. There is no evidence of increased concentration of P^{32} in the lesion. Exposure time was three days. Below: Radioautograph of the same section. Exposure time, four days. Lower: Radioautograph of a 200μ section from the same experiment. Exposure time, 21 days.



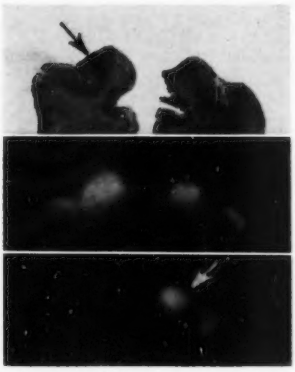


Fig. 4.—Upper: Unstained, dry-frozen section (100μ) of both upper parietal lobes of cat. Arrow shows lesion, produced by insertion of a needle into the cortex and stained vitally with trypan blue. Middle: Radioautograph of same section three hours after application of a P^{32} solution over the cortex. The P^{32} concentration is not increased in the traumatized brain tissue. Exposure time, four days. Lower: Radioautograph of a similar section one hour following intravenous injection of 500μc. of P^{32}. Arrow points to the increased isotopic content within the lesion. Exposure time, eight days.

TABLE 2.—*P^{32} Uptake After Application of the Isotope Solution Over the Parietal Cortex* *

Time elapsed	55 min.	150 min.	200 min.
P^{32} solution	820	1,520	1,150
Cortex			
1 mm. from surface, side of lesion	943	1,105	970
Normal side	835	1,016	1,220
2 mm. from surface, side of lesion	46	99	460
Normal side	38	122	310
3 mm. from surface	6	5	110
Plasma	1.1	0.2	0.5
Cisternal CSF	0	0	0

* Data are given in counts per milligram per minute.
The lesions were situated between the lower part of the 1 mm. zone and the midportion of the 3 mm. zone.

Comment

At the present time the general principle that rules the exchange of ions between CSF and brain tissue is still in doubt. The important fact emerging from these experiments is that no selective concentration of P^{32} is found in the lesion once the isotope has been made equally accessible to injured, as well as normal, tissue. The route by which the isotope arrives at the lesion would be irrelevant if the increased uptake by the lesion were caused by cellular metabolism alone. This finding represents a marked contrast to the situation that prevails after intravascular administration of the isotope.[2,4]

In evaluating the relative importance of increased barrier permeability and difference in metabolism in cerebral lesions, it must be made clear that these two factors are not necessarily controversial and that it is quite arbitrary to explain the increased P^{32} uptake by one single mechanism alone. However, one has to distinguish clearly between *access* to an isotope by a cerebral lesion and its subsequent *utilization* by the cells. We would like to lay emphasis on the first phase, on the increased uptake of the isotope by the lesion from the circulating blood. This is *conditio sine qua non;* without this easy access to the isotope not enough could be acquired for special turnover by the tissue of the lesion.

Our own experiments,[2,4] as well as those of Brierley,[6] show that the peak of the traumatic barrier breakdown is reached immediately after the injury and must be related to direct capillary damage. Microglia changes resulting in macrophage activity develop much later and, consequently, cannot be responsible for the increased isotope uptake by the lesion, although from the point of view of tissue metabolism they probably represent the most vigorous components in the traumatized brain. Ultrasonic lesions are not hemorrhagic. The radioactivity of the blood following intravenous injection of P^{32} does not account for the concentration in the lesion.

A controversy in interpretation involves the various clinical aspects of cerebral P^{32} concentration. Certain forms of experimental virus encephalitis result in an increased P^{32} uptake by the affected parts of the brain.[1,9,10] It was suggested that this was caused by the increased metabolism of the host cells.[1] However, Higginbotham and his co-workers[9] attributed this increased P^{32} exchange between plasma and brain to a nonspecific increase in the permeability of the blood-brain barrier, caused by the inflammation, rather than by a specific metabolic requirement for virus synthesis.

The concentration of radioactive isotopes following intravenous injection in brain tumors represents a difficult problem in interpretation. Relatively little is known of the chemical composition and metabolism of these tumors. Most of the known metabolic activity of cerebral neoplasms does not compare favorably with the metabolism of normal brain. Recently, Selverstone and Moulton[13] called attention to the vigorous P^{32} uptake by the phospholipid fraction of gliomas and concluded on that basis that P^{32} uptake by gliomas is the result of a cellular process alone and not of a breakdown in the blood-brain barrier. Metabolically inert tracers, such as radioactive iodinated serum albumin, are among those whose concentration in brain tumors is not explained by this theory. It is not logical to assume that the selective deposition of various tracers in neoplasms is caused by greatly different principles.

We do not propose to draw conclusions from our findings regarding all aspects of increased isotope uptake by brain tumors. It is obvious that the metabolic requirements and processes of tumor cells differ from those of normal or injured neurons and glia. The metabolism of tumor cells can account for the difference in P^{32} uptake by various phosphate fractions and might add to the total P^{32} uptake by the tumor. However, we wish to emphasize that, in our opinion, an increase in the permeability of the blood-brain barrier is a prerequisite to

any subsequent metabolic process. The change in barrier permeability is nonspecific; it certainly applies to all lesions severe enough to interfere with cerebral capillary permeability.

Summary

The uptake of P^{32} by normal and injured brain tissue was studied in cats by applying the tracer solution directly to the cerebral tissue, excluding thereby vascular channels. Lesions of various size were produced by focused ultrasound. They were placed in one group of experiments in the area of the lateral geniculate body in close proximity to the ambient cistern. In another group of experiments the lesions were placed in the parietal lobe, intra- or subcortically. The gross visualization of the lesions was enhanced by a single intravenous injection of trypan blue.

At from 36 minutes to 3 days after the ultrasonic irradiation, an isotonic P^{32} solution was administered intracisternally in one group and directly over the pia-arachnoid-covered cortex in another group. The animals were killed 10 minutes to 8 hours after the administration of P^{32}.

Changes in the inorganic phosphorus content of the cerebrospinal fluid were measured in relation to large lesions in close vicinity to the cerebrospinal fluid system. The routes and speed of P^{32} distribution along the cerebrospinal fluid pathways and its rate of disappearance from that fluid were studied after cisternal injection.

The rate and extent of P^{32} absorption by the cerebral tissue were determined by radioautography and by direct measurement of radioactivity. Special emphasis was laid on the uptake of P^{32} by the lesion from the nearest cerebrospinal fluid compartment or from the isotope solution applied over the cortex. It was found that there was no difference between the isotope concentration inside the lesion and that of adjacent normal tissue. This represented a marked contrast to previous experiments that demonstrated high uptake of P^{32} when the isotope was administered intravascularly. This observation emphasizes the importance of the blood-brain barrier in cerebral phosphate uptake; the route by which the isotope arrives at the lesion would not be important if the increased uptake by the lesion were caused by cellular metabolism alone.

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Effect of Spatial Summation on Action of Nociceptive Stimuli on the Cerebral Cortex

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Hardy, Wolff, and Goodell [1] found in extensive studies that the threshold of pain in man was independent of the size of the cutaneous area that was stimulated. Whereas temporal and spatial summation processes have a profound influence on the sensory threshold of touch and temperature sensations, the investigations of Hardy and others showed that the pain threshold was lowered by temporal but not by spatial summation. On the contrary, it is well known that both forms of summation influence the intensity and duration of the reflex reactions resulting from nociceptive stimulation. Since this statement is based largely on spinal reflexes, it appeared desirable to investigate the effect of spatial and temporal summations on cerebral reactions induced by nociceptive stimulation.

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Method

Experiments were performed on lightly anesthetized cats prepared under thiopental (Pentothal) and local anesthesia, later supplemented by chondodendron tomentosum extract, purified (Intocostrin). Artificial respiration was used routinely. The electrocorticogram was recorded through silver electrodes, which were in contact with the dura mater. The hypothalamogram was recorded with Hess electrodes. The Offner analyzer was used, as in a previous paper,[2] for the analysis of the cortical potentials. The blood pressure was recorded from the femoral artery. The immersion of the tail or leg in water of 50-70 C served as the nociceptive stimulus.

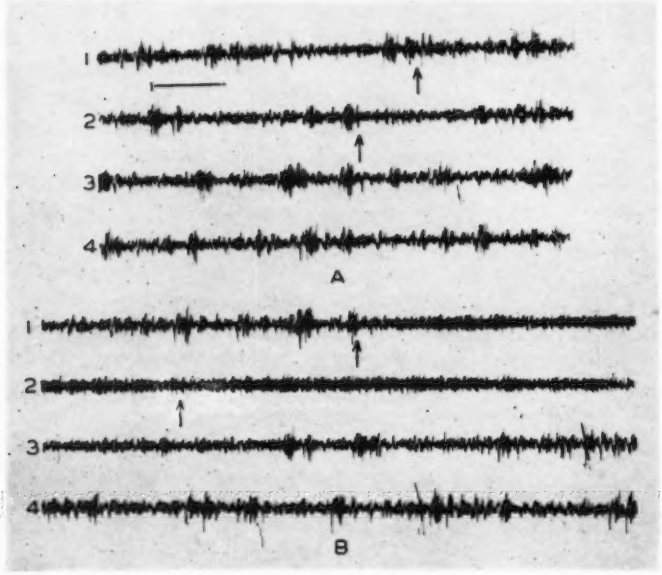

Fig. 1.—Effect of nociceptive stimulation of increasing cutaneous areas on the electrocorticogram of the right motor cortex. *1-4*, continuous records: *A*, 3 cm. of the tail; *B*, 12 cm. of the tail immersed in water of 60 C for 30 seconds (between the arrows). Calibration: 100μv. and 5 seconds.

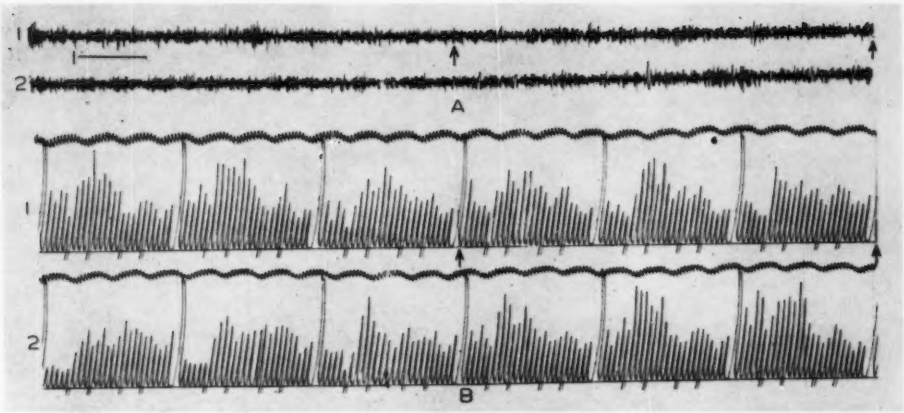

Fig. 2.—Effect of nociceptive stimulation on the electrocorticogram and analysis of the ECG. *1*, *2*, continuous record from left and right motor cortex, blood pressure, and analysis of ECG. Between the arrows 12 cm. of the tail is immersed in water of 50 C for 30 seconds. Calibration as in Figure 1; systolic blood pressure, 164 mm. Hg.

The record showing the analysis consists of 10-second periods separated by large vertical deflections ("epoch markers"). The smaller deflections of the pen between the two epoch markers indicate the relative amplitude of the individual frequency components during this 10-second period. There are four downward deflections, so-called frequency band markers, which divide the frequency spectrum into five groups. The pendeflection pips comprise the following frequencies per second:

First Group: 1.5, 2, 2.5, 3, 3.5; second group: 4 to 7; third group: 8 to 13; fourth group: 14, 15, 16, 18; fifth group: 20, 22, 24, 27, 30.

Results

Figure 1 shows the effect of nociceptive stimulation of cutaneous areas of different sizes on the electrocorticogram (ECG). There was no clear evidence that the stimulus applied to the tip of the tail (3 cm.) altered the ECG, since the grouped potentials persisted during and after the stimulation. When, however, 12 cm. of the tail was stimulated, the ECG record showed a complete disappearance of the grouped potentials during and for some time after the stimulation. The last line of *B* shows that the effect was reversible. This differential action, produced by the immersion of small and large areas of the tail or leg in hot water was repeated many times in the same animal, with similar results. In most experiments the corticogram was analyzed with an Offner analyzer in order to disclose finer details of the nociceptive action.

Figure 2 illustrates the value of cortical analysis for the study of the action of nociceptive stimuli. As the result of a very mild nociceptive stimulus, the ECG did not show distinct alterations. The analyzer indicated, however, that the integrated amplitudes of the slow potentials of the first group, comprising frequencies between 1.5 and 3.5 per second, decreased during the period of stimulation. Even more marked effects appeared in the first two records after stimulation. The integrated amplitudes of the slow potentials decreased still further; and similar changes, although of a less pronounced degree, appeared in the second and third groups (frequency 4-7/sec. and 8-13/sec.), whereas the amplitudes of the last two groups (14-18/sec. and 20-30/sec.) increased slightly. The last part of the analyzed record shows the reversibility of these changes.

If nociceptive stimuli of increasing intensity or duration were applied, the following degrees of suprathreshold effects could be distinguished:

1. Decrease in the amplitude of the slow potentials (1.5/sec.-3.5/sec.).

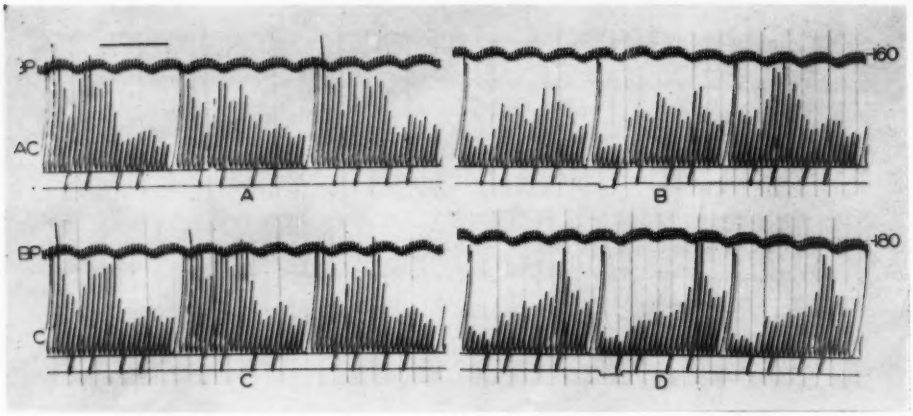

Fig. 3.—Effect of nociceptive stimulation of increasing cutaneous areas on the electrocorticogram of the motor cortex. Blood pressure and record of the analysis. *A, C*: before stimulation. *B, D*: The first period begins 20 seconds after the onset of stimulation. The two following periods were recorded immediately after the period of stimulation. Horizontal line (left upper corner)=5 sec. Top record: immersion of 3 cm. of the tail in water of 60 C for 30 seconds; bottom record: 12 cm. of the tail immersed in water of 60 C for 30 seconds.

2. In addition, a decrease, but to a less pronounced degree, in the amplitude of the potentials of the second and third groups (4/sec.-13/sec.).

3. Appearance of changes described under No. 2 in combination with increases in the integrated amplitude of Group 4 (14/sec.-18/sec.) and Group 5 (20/sec-30/sec.). Strong excitation caused the amplitude of the integrated potentials to increase continually from the slow to the fast potentials, whereas a slightly weaker excitation led to a maximum in the amplitude in the fourth group. Moreover, the duration of the excitatory phenomena increased with increasing intensity of stimulation (after-discharge).

Figure 3 illustrates a typical experiment on the effect of nociceptive stimulation involving a small (*B*) and a large (*D*) area of the tail. The records obtained under control conditions (*A* and *C*) are very similar. The first records in *B* and *D* show the alterations in the integrated potentials that appeared during the last 10 seconds of the period of stimulation. Both records show the fundamental changes produced by the stimulation: The integrated amplitude increased from the first to the fourth group, whereas in the controls the amplitude of the potentials of the first three groups was much greater that that of the fourth group. But there are marked quantitative differences between the first records in *B* and in *D*. First, the indicated changes are much greater in *D* than in *B*; second, the fifth group, when compared with the control records, showed an increased amplitude in *D* but not in *B*, and, third, these changes persist in the two subsequent records in *D*, whereas they become progressively less in *B*.

The greater changes in the ECG produced by nociceptive stimulation of a larger area were frequently accompanied by a larger rise in blood pressure. However, the appearance of the maximal changes in the ECG did not coincide with the maximum of the blood pressure. Moreover, the action on the ECG often persisted after the blood pressure had returned to the control level.

In order to give a complete and accurate account of the changes in the ECG resulting from the application of nociceptive stimuli involving different cutaneous areas, the amplitude of each frequency, as recorded by the Offner analyzer, was measured, and the average for three 10-second periods was determined before stimulation (control) and during and after stimulation. The changes occurring during and after stimulation were expressed in percentage of the control values. Figure 4 illustrates a typical experiment in which a weak nociceptive

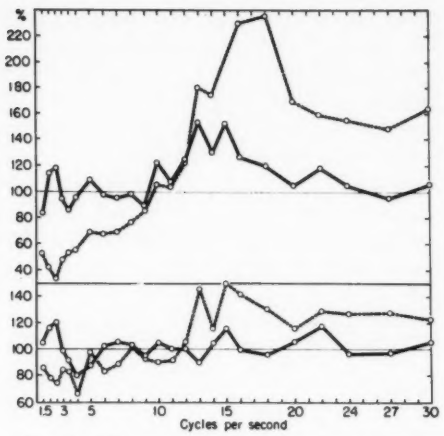

Fig. 4.—Effect of increasing areas of nociceptive stimulation on the electrocorticogram of the motor cortex. Bipolar recording from left and right motor areas. The height of the amplitude of the potentials recorded with the analyzer was averaged for each frequency for three 10-second periods before (control), during, and after the stimulation, expressed in percentages of the control values (ordinate). Abscissa: frequency of the potentials. Lower section: effect during stimulation; upper section: effect after stimulation. Immersion in water of 55 C for 30 seconds of 3 cm. of tail (heavy line) and of 12 cm. of tail (interrupted line).

stimulus (water of 55 C) was applied to the tail. The lower section of the Figure shows the effect recorded during; the upper section that seen after, the stimulation. The immersion of a small area of the tail (heavy line) did not alter the potentials significantly during the 30 seconds of stimulation. The stimulus involving the larger area (interrupted line) showed the typical "shift to the right"; i. e., the integrated amplitudes of potentials of low frequencies decreased, whereas those of the higher frequencies (13/sec. to 30/sec.) increased.[7] The action on these potentials was still greater in the poststimulatory period. There was only a slight increase in the integrated amplitudes when the small area was stimulated, and this increase was confined to frequencies between 12/sec. and 18/sec. On stimulation of the large area, the reduction in the integrated amplitude of the potentials of slow frequencies and the increase in that of high frequencies were very marked.

After strong nociceptive stimulation there was a tendency for a rebound to occur. This was characterized by the appearance of more grouped potentials in the ECG than were seen in the control period. In the analysis the integrated potentials of low frequencies were larger than before stimulation.

It should also be noted that if the hypothalamogram was recorded and analyzed, the changes induced by an increasing area of nociceptive stimulation were similar to those seen in the ECG, but less marked.

Concerning the relation between nociception and the autonomic nervous system, it may be said that with greater degrees of nociceptive stimulation, regardless of whether this involved an increase in area, intensity, or duration of the nociceptive stimulation, increasing degrees of sympathetic excitation appeared, as indicated by the greater rise of the blood pressure and the augmentation of the dilatation of the pupils and of the contraction of the nictitating membranes.

Summary and General Comment

The experiments have shown that an increase in the cutaneous area of noxious stimulation led to an increase in the intensity of the cortical excitation. This was indicated by the disappearance of grouped potentials (asynchrony) and by the appearance of fast potentials at an increased amplitude (recruitment). The frequency analysis of the cortex confirmed this intrepretation. This action could be demonstrated with great regularity even if a stimulus was chosen which was without effect on the cortical potentials when it was applied to a relatively small area. Similar effects were observed when the area and intensity of noxious stimulation were kept constant and the duration of the stimulation was increased. It may, therefore, be said that spatial and temporal summations of nociceptive impulses, as well as an increase in the intensity of the stimulus, cause increasing degrees of cortical excitation.

Earlier studies had shown that the nociceptive stimulation which caused a diffuse excitation of the cortex involved the sympathetic division of the hypothalamus.[3] Moreover, lesions confined to this area [4] or a reduction in its excitability through the intraperitoneal [5] or intrahypothalamic [6] injection of barbiturates diminished or abolished these reactions. In agreement with these observations, it was found that spatial and temporal summation of nociceptive stimuli caused increasing degrees of excitation to appear in the hypothalamogram.

The autonomic reactions which resulted from nociceptive stimulation were augmented under conditions of spatial and temporal summations. This was indicated by the greater contraction of the nictitating membranes, the increased dilatation of the pupils, and the more rapid and prolonged rise of the blood pressure. That the hypothalamic upward and downward discharges resulting from nociceptive stimulation were altered in line with alterations in the sympathetic-hypothalamic excitability seems to be related to the fact that reactions to pain, such as the galvanic reflex, depend on the affective state of the experimental subject and on the excitability of the hypothalamus.[7]

From the above data these conclusions seem to follow:

1. The excitability of the posterior hypothalamus determines the magnitude of the sympathetic reactions and the intensity of the hypothalamic-cortical discharges in response to nociceptive stimuli.

2. At a given state of hypothalamic-sympathetic excitability, the hypothalamic-cortical discharges and the sympathetic reactions increase when the noxious stimulation is augmented. The effects on both upward and downward discharges are similar, regardless of whether the intensity or the duration of the noxious stimulus or the area to which this stimulus is applied is increased.

3. If the findings of Hardy et. al. on the ineffectiveness of spatial summation on the perception of pain are correct and valid for the cat, the following paradoxical assumption seems inevitable: The cortical effects of noxious stimulation involving spatial and temporal summation are similar, but the subjective states are quite dissimilar.

Although our experiments pose rather than solve the problem to determine what physiological mechanisms account for the absence of an increase in the intensity of pain when the area of noxious stimulation is increased, some observations relevant to our present concept of the physiological basis of perception should be mentioned. Since the potentials evoked in a projection area by a specific afferent stimulus are present in deep anesthesia, they cannot be the physiological equivalent of sensation and perception. These potentials are augmented by simultaneous stimulation of the posterior division of the hypothalamus.[9,10] Moreover, it was shown that the unanesthetized cat which does not react to a mild acoustic stimulus under control conditions will follow the source of the sound with the eyes if the hypothalamus is stimulated very lightly at the same time.[8] It was thought therefore that the interaction between the hypothalamic-cortical discharges and the impulses conducted to a projection area via specific afferent paths is essential to the process of perception. For the problem investigated in this paper, it is important that a similar cortical facilitation occurs when the diffuse hypothalamic-cortical discharges induced by nociceptive stimuli interact with specific afferent impulses.[11] In the light of the experiments reported in the present investigation, it is probable, but experimentally not yet proved, that this facilitation increases when the area of noxious stimulation is increased. It will be the task of further investigations to determine whether the human brain follows the reaction pattern described in this study and, if this is the case, to ascertain which cortical processes, if any, will remain constant when a noxious stimulus of a

given intensity is applied to increasing cutaneous areas.*

* It is of interest to note that the spinoreticulothalamic system, to which Bowsher [12] attributes the conduction of impulses associated with the "diffuse, poorly localized pain," is closely related to, or identical with, the hypothalamic-cortical system, which was involved in our investigations.

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Localization of Function in the Corpus Callosum

Visual Gnostic Transfer

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The fibers of the corpus callosum have been described, in general, as coursing with greatest density between homologous cortical loci.[1,2,5,9] Such prominence of homologous fibers in the corpus callosum suggests a functional parcellation within this structure, mirroring, at least in some degree, that found over the related cortical surfaces. However, experimental evidence bearing on functional localization within the corpus callosum has remained sparse.

Physiological studies on the corpus callosum have yielded some data suggestive of functional differentiation within this structure. Electrical stimulation of the commissure caudal to the genu in anesthetized animals has resulted in movements of body parts, the parts involved being dependent on the exact locus of stimulation. Further, stimulation at many other points along the corpus callosum has failed to bring about such motor response.[6,10]

No reports have been published of current application to the corpus callosum in the conscious human, and hence no inference can be drawn as to possible subjective effects which might be associated with such stimulation.

In recent explorations utilizing psychological techniques, it has been possible to demonstrate function for the corpus callosum in the transmission of visual experiential or gnostic data between the hemispheres. Specifically, cats with the crossed retinal fibers destroyed were taught simple visual-pattern discriminations with a mask occluding one eye. On shifting the mask, performance with the second, untrained eye was nearly perfect in those cats with the corpus callosum intact, but was at a chance level in those which had had, in addition, section of the corpus callosum prior to training.[7,8,11]

With a demonstration of a clearly defined function for the corpus callosum, it seemed desirable to determine whether this function is localized to a particular part of the nerve bundle or whether, instead, it is mediated by the commissure as a whole. Therefore, in the present study, the experiments were extended to cats having only partial lesions of the corpus callosum in addition to chiasma section.

Methods

Animals.—Ten cats were used. All were young but fully grown animals with no prior experience in formal psychological training or other laboratory testing.

Procedures.—The crossed retinal fibers were first sectioned at the optic chiasma, using the transbuccal approach previously described.[7] After recovery from this procedure the corpus callosum was partially divided through an extensive unilateral craniotomy, as outlined in another communication.[8] One group, of four cats, sustained varied section of the anterior corpus callosum. The extent of section in each of these cats is described in Column 2 of Table 1 in terms of millimeters sectioned measured from the anterior extremity of the genu backward. Another group, of six cats, sustained varied section posteriorly. Column 2 of Table 2 describes the extent of section in these splenium-sectioned cats, again, in terms of millimeters sectioned, but as measured from the posterior extremity at the splenial tip forward. The proportion of the

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total anteroposterior extent of the corpus callosum included in the partial lesion in each case is described in parentheses as a percentage figure. This latter designation is recognized as a crude but desirable relative measurement.

Transfer of a single-pattern discrimination was studied, the test patterns of which are illustrated in Figure 1. The pattern in Column *a* was arbitrarily assigned a positive and that in Column *b* a negative value. Prior experiments carried out with these patterns have indicated that cats have no initial preference for either of the two patterns of the pair.

The same training box and procedures were used as described earlier.[7] In establishing the discrimination, the two patterns of the pair were presented side by side, and the cats were trained to choose the positive (*a*) pattern. Correct choice was rewarded by a morsel of food; incorrect choice was mildly punished by verbal reprimand and non-

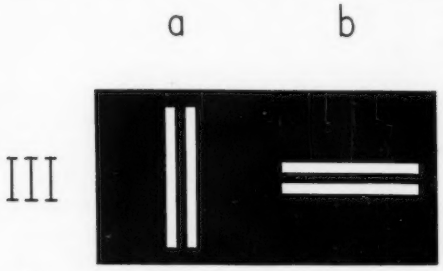

Fig. 1.—Paired patterns of Discrimination III. The vertical lines of Column *a* were abitrarily chosen as the positive figure.

reward. The patterns were alternated from side to side according to a chance sequence to avoid development of side preference.[8] During the periods of training light was excluded from the left eye by the use of a black rubber mask, held snugly in place by ties to a leather collar. The cats attained a performance of 34 or more trials correct in 40 after an average of 320 training trials, with a scatter between the extremes of 240 and 480 such trials. The response was then considered to be established but was further stabilized by giving 400 additional overtraining trials, run in sessions of 40 a day. The performance on the last day of overtraining was 40 correct in 40 in all instances but two, in which performance was 35 (Cnt) and 37 (Blc). On completion of overtraining, the mask was shifted to the right eye, and tests of interocular transfer were carried out with the cat, using the "untrained," left eye for the first time. Where immediate recall was not seen, the response was reinstated by additional training with the cat using the "untrained" eye. In Columns 3 and 4 of Tables 1 and 2 are listed the performances of each cat on the first and second days of transfer testing.

TABLE 1.—*Transfer Performance in Chiasma-Sectioned Cats with Division of Anterior Corpus Callosum*

Cat	Extent of Section	Test Performances (Correct in 40) Day 1	Day 2
Btt	12.3 mm. (70%)	32	38
Brd	11.4 mm. (75%)	39	40
Tll	11.7 mm. (77%)	37	38
Gry	15.0 mm. (87%)	24	13

These performances may be compared with those of five chiasma-sectioned cats and of four chiasma- and callosum-sectioned cats, in which average performances of each group on the first 40 transfer trials with the same discrimination III were 38 and 20 correct, respectively (Myers[7,8]).

The four graphs of Figure 2 compare rate of learning with the initially trained, right eye and with the "untrained," left eye in four cats, one (*Gry*) with anterior and three (*Blk, Blc,* and *Gbb*) with posterior section of the corpus callosum.

Anatomical Controls.—At the end of the experiment, the animals were killed with pentobarbital and then perfused with 10% formalin. The completeness of chiasma section was checked and the extent of callosum destruction determined by measurements on the formalin-fixed brains. For purposes of comparison it was considered desirable to state the proportion of the total corpus callosum sectioned rather than to rely alone on the absolute measurements, inasmuch as the amount of tissue shrinkage was significantly variable among the specimens, due to variation of storage times in fixative. The extent of corpus callosum sectioned in each cat may be seen from Column 2 of Tables 1 and 2. Fibers of the psalterium (commissure of the fornix) were of necessity destroyed at the time of callosum section because of their close apposition to the inferior surface of this nerve band.

TABLE 2.—*Transfer Performance in Chiasma-Sectioned Cats with Division of Posterior Corpus Callosum*

Cat	Extent of Section	Test Performances (Correct in 40) Day 1	Day 2
Cnt	4.8 mm. (26%)	33	38
Cto	5.3 mm. (37%)	35	39
Wld	7.3 mm. (42%)	33	38
Blk	6.2 mm. (44%)	22	20
Blc	9.0 mm. (53%)	23	28
Gbb	11.8 mm. (68%)	21	25

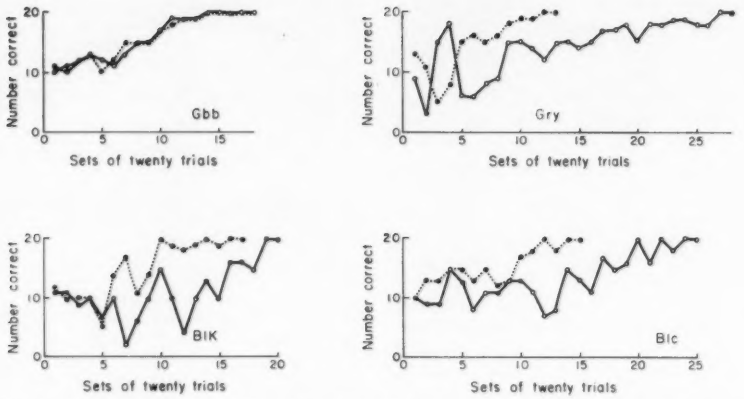

Fig. 2.—Graphs comparing rate of learning of the two eyes on Discrimination III in four cats. Initial learning with the right eye is represented by the solid line, and relearning with the left eye, by the broken line. Extent of destruction of the corpus callosum in each case may be seen by reference to Tables 1 and 2. *Gbb* shows no saving in relearning with the untrained eye, while some very slight saving is suggested from the curves of *Gry*, *Blk*, and *Blc*. Cat *Gbb* was trained and tested by a worker other than the one handling *Gry*, *Blk*, and *Blc*.

Results and Comment

Transection of as much as 75% to 77% of the corpus callosum in its anterior extent does not interfere significantly with interocular transfer of simple Discrimination III, as seen by the high-level performance on tests with the untrained eye (Brd and Tll, Table 1). It is only when the section includes up to 85% of the commissure anteriorly that there is interruption of the transfer process (Gry, Table 1, and graph of *Gry*, Fig. 2). On the other hand, section of as little as 44% of the corpus callosum posteriorly completely, or nearly completely, interferes with contralateral recall (Table 2, and graphs of *Blk*, *Blc*, and *Gbb*, Fig. 2). In addition, there are signs of some interference in transfer with all posterior lesions, including the least one, of 26%.

These results indicate a clearly defined posterior localization of the visual gnostic transfer process in the corpus callosum. More anterior fibers do not seem to sustain transfer themselves nor does their destruction compromise transfer.

On closer scrutiny of the data, a second aspect of the localization process emerges; i. e., within the involved posterior segment there is a certain degree of equipotentiality of function. Cats Cnt and Cto were able to transfer Discrimination III with the posterior fourth to third of the corpus callosum destroyed; that is, with the *anterior* half to fifth of the splenial segment functional, while Brd and Tll succeeded in such visual transfer with the anterior three-fourths of the corpus callosum destroyed or with the *posterior* half of the splenial segment functional. Thus, in different cats, entirely different parts of the posterior "visual" segment were able to mediate transfer of the selfsame discrimination problem.

The length of the preserved segment of the posterior corpus callosum in Cats Tll and Brd was 3.5 and 4.0 mm., respectively, while in Gry it was only 2.2 mm. Cats Tll and Brd were able to transfer Discrimination III as well as cats with intact corpus callosum. Gry, on the other hand, showed failure of transfer, with, however, some indication of slight saving in trials to relearn (graph for Gry). Calculations made from measurements of the preserved callosal bundles in these cats gave cross-sectional areas of close to 5 and 6 sq. mm. for Tll and Brd, respectively, and of 3.5 sq. mm. for Gry. A Haggquist preparation was made of the relevant splenial region of a normal cat. Fi-

ber counts of representative areas averaged 700,000 fibers per square millimeter, giving an approximate number of 3,500,000 to 4,000,000 nerve fibers remaining in the preserved splenial segment for Tll and Brd and of 2,500,000 fibers for Gry. If it were assumed that all the fibers of the preserved segment were involved in the gnostic intercommunication, something between 2,500,000 and 3,500,000 fibers would be involved in successful transfer of Discrimination III. However, this assumption seems unlikely, inasmuch as cortical surfaces thought to be nonvisual in function are also interconnected by callosal fibers in the region of the splenial tip (posterior part of gyrus splenialis and parts of gyri suprasylvius posterior and ectosylvius posterior). Furthermore, it is probable that fibers running between cortical surfaces, thought to be visual in function, may be involved in activities that are not gnostic in import. Reference may be made to elicitation of eye movements in the monkey with stimulation of the corpus callosum in the region of the splenium.[10] From these considerations it seems likely that the number of fibers involved in the visual gnostic transfer (of Discrimination III) is less than the 2,500,000 to 3,000,000 fibers estimated above.

Summary

Ten cats sustained section of the crossed retinal fibers at the chiasma and, in addition, division of varied extents of the anterior or posterior corpus callosum. After these procedures the cats were taught a simple visual-pattern discrimination response with a mask covering one eye. Recall tests were then carried out with the cats using their previously untrained eye. Cats with anterior section of the corpus callosum showed good recall on these tests, while those with sufficiently large sections posteriorly failed completely. The findings indicate a gross posterior localization of the visual gnostic transfer process in the corpus callosum. However, it was evident from the data that within the involved posterior sector there was considerable functional equivalence between its different parts, transfer of the same discrimination problem being supported by relatively small segments regardless of their position. A gross estimate of maximal number of nerve fibers involved in the transfer process was made from fiber counts.

Dr. W. J. H. Nauta furnished Haggquist preparations of the posterior corpus callosum.

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Bilateral Resections of Frontal Granular Cortex

Factors Influencing Delayed Response and Discrimination Performance in Monkeys

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Frontal granular cortex in the monkey has been shown to possess a functional specificity rivaled only by sensory and motor cortex. The delayed response, interpreted by Jacobsen as a test of immediate memory, is a reliable indicator of bilateral frontal-lobe damage in infrahuman primates.[1,9,19] Lesions in other parts of the cerebrum affect performance on the delayed response only minimally and inconsistently.[4,12,18]

Following the original observations by Jacobsen, it was shown that minor variations in the test procedure, variations which seem to leave the desideratum of the test intact, affect the sensitivity of the test. One of these demonstrations was that monkeys with bilateral frontal-lobe resections can be made to respond effectively on the delayed response when retained in darkness during the delay period.[14] Another showed the effectiveness of a predelay reward in improving postoperative delayed-response performance.[6] Since the delay qua delay remains unaffected by the variations, observations such as these have led investigators to question whether the postoperative deficit should be conceptualized as one of immediate memory. A neglected possibility is that there is a multiplicity of ways by which monkeys can perform efficiently on the delayed-response test. Remembering which cup was baited is only one way. The monkey may derive cues at the time of response from his posture or position in space without the need to carry the solution centrally. One way to attack this problem is to apply behavioral tests with known relationship to the delayed response and compare the postoperative effects on the two tasks. This approach was initiated by Jacobsen and Nissen in their study of delayed alternation.[10] Another approach is to reanalyze the requirements for solution of the delayed response. Does the animal provide himself with cues that are operative at the time of response? The present experiment focuses upon efficiency of delayed-response performance and level of locomotor activity when normals and bifrontal-lobectomized monkeys are retained in darkness during the delay period. Since the essential of the delayed response, namely, the interpolated delay, remains an integral part of the test, these data emphasize the need to reexamine the requirements for solution of the delayed response.

In addition to the specific "immediate memory function," there have been scattered claims of nonspecific or cognitive functions of the frontal lobes, functions which are apparently shared with the rest of the cerebrum. According to these claims, bifrontal-lobe resections are apt to produce visual-discrimination disturbances [8] and auditory discrimination deficits.[1] How consistent these disturbances are has never been determined. Curiously, a similar functional nonspecificity has been demonstrated for sensory-motor tissue, particularly for striate cortex, whose nonvisual functions can be studied after peripheral blinding.[18] Another

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aim of the present study is to reexamine experimentally the discrimination impairment after bilateral frontal-granular-cortex resections. A tactile problem was chosen for study, but there were incidental observations of visual discrimination as well.

The functional specificity of frontal granular cortex will be examined experimentally in this report, and an interpretation will be offered to account for the multiplicity and apparent inconsistency of effects following frontal-lobe damage. It will be argued that the existing evidence does not rule out postoperative immediate memory impairment as one factor in the delayed response disturbance.

Method

Subjects.—Five immature female rhesus monkeys (Macaca mulatta) served as subjects. All were experimentally naïve but tame enough to open the experimenter's clenched hand in order to take food from it.

Apparatus and Procedure.—Three tests were applied preoperatively and postoperatively: tactile discrimination, visual discrimination, and indirect delayed response based upon the visual discrimination. The usual two-choice discrimination apparatus and procedure was employed.[4]

The tactile discrimination was run in total darkness. Experimental observation was made possible with the aid of a Snooperscope, a device which transforms infrared light to light visible only to the experimenter through a viewer.[20] The manipulanda consisted of a faucet knob and a 35-mm. film container, both mounted on inverted cups. The subject was required to identify the positive object by palpation, to displace it, and to secure the food under it.

For the visual discrimination, two 7-watt bulbs, blackened to reduce the intensity, were mounted directly over the two food cups. The baited cup was thus dimly illuminated during each trial by the bulb immediately above. The procedure was identical for the delayed response, except that the stimulus light was extinguished before response was permitted. Scores for minimal delay and five seconds' delay were recorded separately. "Minimal delay" indicates that the stimulus light was displayed for three seconds; the opaque screen was then lowered and raised immediately to permit choice. "Five seconds' delay" indicates that the opaque screen was not raised for five seconds. The stimulus light provided sufficient illumination for experimental observation, and a desk lamp served for recording purposes. In addition, a 60-watt bulb was mounted directly over the subject and was used for the "light-interpolation" condition during the five seconds' delay trials.

The subject was placed on a hinged platform behind the opaque screen. Locomotor movement from back to front of the test cage and vice versa actuated a counter. Thus, a gross measure of locomotor activity was obtained during the delay periods. This apparatus was designed as a simplified version of Malmo's and duplicated all its essential features.[14]

Each session consisted of 30 trials. The criterion for initial learning and postoperative relearning of each test item was 90% correct responses in 30 trials. Preoperative and postoperative retention tests consisted of 60 trials (or two sessions) on each task. Noncorrection technique was employed.

Initially, all monkeys were trained in total darkness to displace identical objects from the tray in order to obtain food. Formal training was initiated only after the monkey had learned to respond with alacrity when the opaque screen was raised. The preoperative training sequence of tasks was as follows: tactile discrimination, visual discrimination, delayed response with minimal delay, and delayed response with five seconds' delay.

Preoperative retention tests were carried out after a 13-day rest period, and postoperative retention tests were run after a 13-day recovery period. Sixty trials were given on each of the tasks: tactile discrimination, delayed response with minimal delay, delayed response with five seconds' delay without light interpolation, and delayed response with five seconds' delay with light interpolation, alternated in blocks of six trials. The preoperative level of performance on conditions both of light and no-light interpolation was accordingly obtained. Since performance on the delayed response with

TABLE 1.—*Steps in Training and Testing After Initial Postoperative Disturbance Was Demonstrated*

	Postoperative Sequence 3-7 Wk. After Operation			Prekilling Sequence 12-17 Wk. After Operation
Tasks	1	2	3	4
Visual discrimination	Test Train	--	--	Train
Delayed response with minimal delay	Test	Train	--	Train
Delayed response with 5 sec. delay	Test *	Test †	Train ‡ Test	Train Test

* Monkeys 1, 3, and 4.
† Monkeys 1, 3, 4, and 5.
‡ Monkey 4.

minimal delay was greatly affected, the postoperative level of performance on conditions both of light and no-light interpolation could not be obtained, and the experimental design could not be realized to completion. The procedure was therefore extended as the experiment progressed, and the design was guided by the observed performance level. Table 1 lists the steps in postoperative training and testing after the initial disturbance was demonstrated. The desideratum was a comparison of performance with and without light interpolation on the delayed response for all five monkeys, and this could be realized only after postoperative training on the delayed response itself.

Surgery and Histology.—All operations were performed under deep pentobarbital anesthesia with aseptic precautions. The lesions were bilateral and produced in one stage. A coronal incision extending bilaterally was made in the scalp immediately in front of the coronal suture; an osteoplastic flap was turned, and the dura was incised to expose the frontal lobes anterior to the fissure of Rolando. Aspiration was used to remove the cortical tissue, and the wounds were sutured in anatomic layers. The lesion extended anteriorly from the bend of the arcuate sulcus, followed the two branches as boundaries wherever possible, and included the frontal pole.

After the conclusion of testing, the monkeys were perfused via the carotid artery with isotonic saline and 10% formalin, and their brains were fixed, dehydrated, and embedded in paraffin. Serial sections 25μ thick were cut, and every 20th section was saved and stained with cresyl violet. Representative sections through the primary lesion were checked histologically, and retrograde degeneration in the thalamus was sketched.

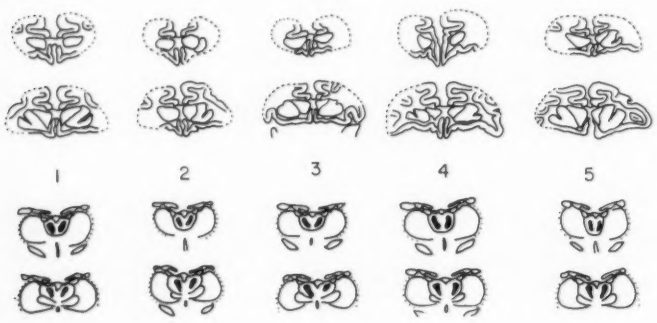
The histological study confirmed the locus and size of the primary lesion. The lateral surface of the frontal lobes between the two branches of the arcuate sulcus was removed in all monkeys. In most instances, the depth of sulcus principalis was spared. In one monkey (No. 3) the lateral portions of the orbital surface were damaged. The basal ganglia were found to be unaffected in all monkeys.

The extent of cortical removal and retrograde degeneration in the thalamus are shown on representative sections in the accompanying Figure. Massive degeneration was seen in the magnocellular and parvocellular parts of nucleus medialis dorsalis in all monkeys. No other nuclei were affected. A small area of degeneration in the right lateral geniculate body of Monkey 1 cannot be understood on the basis of the primary lesion. The lesions in all monkeys were judged to be consistent in respect to locus and size.

Results

All monkeys made a good recovery within the two-week postoperative period. There was no paretic stance or gait. The only overt symptom of cortical deficit was intense locomotor activity or reactivity, which was first seen within a few days after operation. In general, the behavioral disturbance in the test situation was much severer than had been anticipated. The disturbance was reflected on all tests during all phases of study.

Retention scores on the tactile discrimination are listed in Table 2. The postoperative performance of four of the five monkeys was not significantly better than chance. In contrast, preoperative retention was near or above the 90% criterial level. Retraining scores for the three monkeys retrained were no better than initial learning scores, and this further illustrates the level of disturbance. On the other hand, the tactile-discrimination performance of one monkey (No. 4) was not affected by the operation.



Record of lesions shown on representative coronal sections. Above, extent of cortical removals; below, retrograde changes in nucleus medialis dorsalis of the thalamus.

TABLE 2.—*Tactile Discrimination*

Animal	Retention : % Correct in 60 Trials		Postoperative Retraining: No. of Sessions to Return to Criterial Level of Performance
	Preoperative	Postoperative	
1	87	60	6
2	100	63	--
3	100	58	8 *
4	93	98 †	0
5	92	62	8 *

* Asterisk indicates that criterion was not met within 8 sessions, or 240 trials.

† Significant χ^2=0.01 with 1 d. f.

TABLE 3.—*Delayed Response: Minimal Delay*

Animal	Retention: % Correct in 60 Trials			Retraining: No. of Sessions to Return to Criterial Level of Performance	
	Preoperative	Postoperative	Postoperative After Retraining on Visual Discrimination	Postoperative	Prekilling
1	88	65	72 *	9	3
2	92	58	47	--	6
3	93	78 *	78 *	10	1
4	95	58	75 *	2	0
5	97	55	63	4	2

* Significant χ^2=0.01 with 1 d. f.

Retention scores on the delayed response with minimal delay are illustrated in Table 3. Again, the postoperative performance of four of the five monkeys was not much above chance, and, again, preoperative retention was near or above the 90% criterial level.

The poor postoperative performance on the delayed response with minimal delay precluded extensive testing on the delayed response with five seconds' delay. The most promising monkey (No. 3) was tested, and her postoperative performance on both conditions of light and no-light interpolation was near chance (Table 4).

Henceforward, the design of the experiment was guided by the observed performance level. The first step was to return to the visual discrimination for retesting and retraining. As can be seen in Table 5, only two of the monkeys performed at better than chance level on the visual discrimination, and retraining to the 90% level required from one to eight sessions. Even after this retraining, two monkeys still failed on the delayed response with minimal delay (Table 3, Column 3), and the three monkeys that did improve again failed on the delayed response with five seconds' delay (Table 4, Column 3).

For the second step, it was necessary to retrain to 90% efficiency on the delayed response with minimal delay and to test for resultant improvement on the delayed response with five seconds' delay. Retraining was accomplished within 2 to 10 sessions in the four monkeys studied (Table 3, Column 4), but the efficiency with minimal delay did not produce any significant improvement in performance on five seconds' delay (Table 4, Column 4).

The third step consisted of retraining the monkey with the best over-all performance,

TABLE 4.—*Delayed Response: Five Seconds' Delay*

Animal	Retention: Per Cent Correct in 60 Trials											
	Preoperative		Postoperative		Postoperative, After Training on Visual Discrimination		Postoperative, After Training on Delayed Response with Minimal Delay		Postoperative, After Training on Delayed Response with Five Seconds' Delay		Prekilling	
	Light	No Light	Light	No Light	Light	No Light	Light	No Light	Light	No Light	Light	No Light
1	85	85	--	--	38	57	58	55	--	--	51	81 *
2	80	92	--	--	--	--	--	--	--	--	58	77 *
3	97	93	58	57	45	47	60	60	--	--	81 *	99 *
4	97	100	--	--	48	42	52	62	50	77 *	65	87 *
5	83	93	--	--	--	--	52	52	--	--	57	90 *

* Significant χ^2 = 0.01 with 1 d. f.

TABLE 5.—*Visual Discrimination*

Animal	Retention: % Correct in 60 Trials	Retraining: No. of Sessions to Return to Criterial Level of Performance	
	Postoperative	Postoperative	Prekilling
1	53	2	6
2	82 *	6	5
3	77 *	5	8
4	57	1	4
5	52	8	8

* Significant $\chi^2=0.01$ with 1 d. f.

TABLE 6.—*Mean Locomotor Activity During Delayed Response Test with Five Seconds' Delay*

Preoperative *		Postoperative After Training on Delayed Response with Minimal Delay †		Postoperative After Training on Delayed Response with 5 Sec. Delay ‡	
Light	No Light	Light	No Light	Light	No Light
0.71	0.64	9.6	9.9	7.34	6.86

* Mean activity for four monkeys.
† Mean activity for four monkeys.
‡ Activity for one monkey.

Monkey 4, on the delayed response with five seconds' delay. The resultant test score for the condition of no-light interpolation improved somewhat (Table 4, Column 5).

The fourth, and final, step was initiated three months after operation. All monkeys were again retrained on the visual discrimination, followed by the delayed response with minimal delay, and ending with the delayed response with five seconds' delay under conditions of light and no-light interpolation. The visual discrimination habit was again lost, and no savings were apparent in reacquisition (Table 5, Column 3). This training appeared to reduce the number of sessions necessary to return to criterial level of performance on the delayed response with minimal delay, but had no apparent effect upon performance with five seconds' delay (Table 3, Column 5). It was still necessary to give 10 to 26 sessions of training on the delayed response with five seconds' delay before all monkeys performed at the 90% level of efficiency. The final performance under conditions of light and no-light interpolation for all five monkeys is shown in the last column of Table 4. It can be seen that prekilling performance is consistently superior under the condition of no-light interpolation. With a t of 8 and 4 degrees of freedom, the difference is significant at beyond the 0.01 level of confidence.

The postoperative locomotor activity during delayed-response testing showed a fourteenfold increase over the preoperative level (Table 6). This increase was maintained with only a slight reduction after retraining on the delayed response with five seconds' delay.

No measure of locomotor activity was obtained during the prekilling testing. However, the protocols suggest that the intense locomotor activity in Monkeys 1, 2, and 3 was reduced during the five seconds' delay periods, especially under the condition of no-light interpolation. Moreover, four of the five monkeys clearly adopted some artifice which presumably aided them in performing effectively on the delayed response. Monkeys 1 and 3 learned to position themselves during the delay in front of the baited food well. Monkeys 4 and 5 were apt to circle differentially according to which food well was baited: counterclockwise when the left food well was baited, clockwise when the right food well was baited. The behavior of Monkey 2 in the test situation did not reveal the adoption of a mnemonic device to which her performance could be related.

Comment

The magnitude of the postoperative discrimination disturbance was unexpected. Both tactile- and visual-discrimination habits were affected by the operation. Discrimination disturbances have not commonly been observed in monkeys with bilateral frontal-granular-cortex resections. There are, however, the systematic observations of Blum, who reported loss of an auditory-discrimination habit in three or four of his six monkeys operated on.[1] Further suggestive evidence of discrimination disturbances fol-

lowing bifrontal resection is cited in the review by Chow and Hutt.[5]

This discrimination disturbance seems to be related to the response sterotypy or perseveration seen in monkeys after operation. More frequently than not, this stereotypy manifested itself in the position habit so commonly observed in surgically treated animals. In some monkeys, the intense circling sequence was broken when the opaque screen was raised, only to have the monkey dash to the nearest food well. Curiously, the behavior often suggested that the monkey knew that she was responding incorrectly: She would continue to circle after having displaced the food cup and would not grope for food when in darkness.

This interpretation of the discrimination disturbance in the frontal-lobectomized monkey differs from the usual interpretation of the corresponding disturbances following inferotemporal and postcentral resections. No relation is seen between the present discrimination disturbances and impaired sensitivity or associative dysfunction, but, rather, a third, nonspecific factor appears, which is at present poorly understood.[12]

The magnitude of the delayed-response disturbances was also unexpected. Performance with minimal delays was affected by the operation. This disturbance cannot be attributed to the discrimination loss, because performance was not improved appreciably after reacquisition of the visual discrimination. On the other hand, it should be noted that effective performance on the delayed response was subsequently restored in the monkeys operated on. Prolonged training reinstated efficient performance on the delayed response with minimal delay. For five seconds' delay, training alone on the visual discrimination, or even on the delayed response with minimal delay, was insufficient to reinstate efficient performance; detention in darkness during the delay period was found to be a necessary condition.

Do these data rule out the interpretation of postoperative immediate memory impairment? It is argued here that there are at least three orders of disturbance following bilateral frontal-granular-cortex resections. One is the specific disturbance Jacobsen labeled immediate memory impairment (defined as the inability to respond differentially to cues that are not present at the moment of choice). This impairment is directly related to the primary lesion [19] and is permanent. The second is a more general defect, usually described as stereotypy, or in the present, more restricted context, as an exaggerated tendency to respond to spatial cues. This disturbance seems to follow sufficiently large lesions to any part of the cerebrum, shows up best on discrimination problems, and diminishes over time. The third is a chronic vasodilation of the skin,[13] producing a heat loss which can be compensated for by the locomotor hyperactivity. This disturbance follows lateral surface lesions, as well as the orbital lesions emphasized by Fulton.[7]

What is the basis of solution of the delayed response? The early interpretations emphasized the absence of differential cues at the moment of response. It was argued that the differential cues at the time of baiting are replaced by a central process which guides behavior at the moment of choice. However, it became clear that the animal may furnish itself with differential cues which span the time gap and guide the response. Animals have been observed to position themselves before the positive food cup and wait until choice was permitted. There are other possible methods of solution. Two monkeys in the present group circled differentially, clockwise when the right cup was baited and counterclockwise when the left cup was baited. Another monkey, not included in this study, was observed in total darkness following frontal-lobe resections, and its behavior suggested proprioceptive impairment.[21] It is possible that differential muscular tension or some such mediational cue may span the delay. This view can be tested in preparations with high cervical transection of the posterior columns and destruction of the labyrinth.

Thus, there is a multiplicity of ways by which monkeys can perform efficiently on the delayed response. Remembering which cup was baited, that is, carrying the solution centrally, is only one way, and frontal-lobectomized monkeys do not have this solution available to them. Yet the surgically treated monkey can perform efficiently as early as three months after operation, according to the present data. If he were not so active, the surgical monkey might position himself, and this solution can be adopted either following specific training or following prolonged postoperative recovery. Or the monkey may circle systematically.

Jacobsen and his critics overlooked the possibility that the delayed response can be solved in diverse ways. The interpretation of immediate memory impairment seems correct as far as it goes. According to the present argument, the experimental conditions that have been offered as ruling out this interpretation simply demonstrated that alternative solutions of the delayed response are possible.

Finan showed that a predelay reward increased the efficiency of postoperative performance.[6] According to the interpretation offered here, this procedure probably elicited a positional response. Finan's monkeys suffered an impairment of immediate memory, as all frontal-lobectomized monkeys do, but their postoperative training aided them to adopt a stationary position in front of the correct cup and to respond correctly thereby.

Malmo demonstrated that events during the delay period affect postoperative performance.[14] If the delayed response is run under conditions of reduced illumination, more efficient performance by surgically treated monkeys is elicited. Contrariwise, performance fails under conditions of increased illumination level. These observations have now been confirmed by the present study. Malmo attempted to relate these data to principles of learning by suggesting that after operation monkeys are more susceptible to retroactive inhibition. This does not rule out an impairment of immediate memory. Rather, it defines the conditions under which immediate memory is more or less likely to be affected. Malmo's interpretation should be extended. Certainly, events during the delay might affect subsequent performance, but so would more remote events, such as performance on the preceding trials. Lashley expressed this when he wrote that the delayed response involves the establishment of a succession of conflicting or interfering habits.[12] Confusion of successive "dated" memories may be a major cause of the difficulty of this task. Malmo's data can be interpreted as follows: Under conditions of low illumination, the surgically treated monkey tends to be less active.[11] This has been confirmed in the present study, as well as by observations on bifrontal-lobectomized monkeys that had had enucleation.[21] Thus, Malmo's monkeys could have performed efficiently in darkness by adopting a mnemonic device like positioning. Malmo thought this possibility unlikely, but his data were equivocal on this point.

The present hypothesis interprets "recovery" on the delayed response[3] as compensation for the immediate memory impairment. The monkey tends to circle less and can more easily be persuaded to position himself in the delayed-response situation. This interpretation is supported in part by the present data, that recovery of efficiency can be demonstrated as early as three months after surgery, provided that the monkey is given intensive training to adopt a solution, such as positioning. The same interpretation can be applied to the sedation,[2,22] fasting, and temperature[22] data. In general, any condition tending to calm the monkey or reduce locomotor activity might be expected to increase performance efficiency by permitting the adoption of helpful mnemonic devices.

Nissen et al. have suggested that "the loss of the delayed response ability after bilateral ablation of the frontal areas should be interpreted as a failure to form associations which involve symbolic responses rather than a diminution of memory. The operated animal cannot forget what it has not learned."[24] However, it has been shown

that the surgically treated animal has in fact learned. Successful performance at minimal delay does not ensure successful performance at five seconds' delay. This can only mean that the animal has learned and does forget.

In conclusion, there is more than one basis for solution of the delayed response. The normal monkey may remember which cup was baited, but need not in order to respond effectively. He may position himself, or he may circle differentially, or he may respond to proprioceptive cues. The surgically treated monkey, who has grave difficulty remembering which cup was baited, can still be trained to adopt a solution which provides him with differential cues at the time of response, or he may develop one spontaneously. Whether the successful performance of surgical monkeys with the go-no-go technique of Mishkin [15] or the matching-from-sample technique of Harlow [23] depends upon the adoption of peripheral mnemonic devices, or self-generated differential cues should be checked with an eye to the appearance of unexpected solutions.

Summary

Effects of bilateral frontal-granular-cortex resections in monkeys included disturbances in tactile and visual discriminations in four of five subjects, and impairment on the delayed response even with minimal delays.

Retraining to the preoperative level of efficiency with minimal delay does not improve efficiency with five seconds' delay.

Surgically treated monkeys can nevertheless be retrained to perform effectively on the delayed response. Mnemonic devices, such as positioning, account for this apparent recovery.

Light interpolation during the delay interval is apt to reduce efficiency of performance of the surgical monkey, but not of the intact monkey.

Locomotor activity in the test situation is greatly increased after the operation. Reducing the illumination tends to reduce the level of activity.

It is argued that three factors at least are operative in producing the behavioral disturbances: immediate memory impairment, exaggerated tendency to respond to spatial cues, and chronic vasodilation.

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Ictal Emotions Occurring in Temporal Lobe Dysfunction

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As early as 1879 Jackson [1,2] described the feelings of fear associated with an epigastric aura. He felt that this emotion was an integrated part of an epileptic attack. Only during the past 20 years have neurologists and some psychiatrists paid further attention to certain emotional phenomena which may occur during an epileptic aura or (in combination with motor and/or sensory manifestations) during an epileptic discharge. Emotional phenomena may even be experienced as the only manifestations of clinical or subclinical epileptic seizures, or they may occur as a result of after-discharges following manifest seizures.

Penfield and Jasper [3] have pointed out that patients afflicted with temporal lobe epilepsy are prone to experience "emotions." These authors even evoked emotional reactions, such as feelings of fear, fright, and terror—unrelated to environmental factors—by electrical stimulation of certain temporal lobe areas. "These emotions of fear are not simple fear that an attack is about to come on. Such foreboding might well be associated with any aura. The ictal emotion is produced as a distinct experience and is the result of localized cortical discharge." [3]

In 1948 we began observing a patient who had severe emotional depressions associated with uncinate seizures. By 1954 (Weil,[4] 1955), we had observed six subjects who experienced paroxysmal depressive reactions lasting from hours to weeks and whose main seizure manifestations consisted of uncinate attacks and temporal lobe automatisms. These depressive attacks preceded or followed seizures, or occurred paroxysmally in the "free interval" between seizures. We also noted that accompanying olfactory hallucinations ceased once the depression subsided. We postulated, at that time, that this particular type of depressive reaction might be due to subclinical "hippocampal-amygdaloid-temporal lobe" epilepsy and/ or to after-discharges from the same structures following manifest seizure activation. By 1955 (Weil,[5] 1956) we had observed 11 patients with "ictal emotions," 7 of whom had paroxysmal depressive reactions, whereas 4 subjects had episodes of paroxysmal fear or "isolated anxiety." These anxiety attacks seemed to bear a relation to "firing" of the temporal lobe *cortex*, as demonstrated by our own serial electroencephalographic observations and in the same way as originally described by Penfield and Jasper.[3] The emotional experiences, i. e., fear, depression, anger, and rage, are unrelated to environmental factors, lasting for hours to weeks (particularly in "ictal depressions"), and are characterized by sudden occurrence and usually equally abrupt disappearance. These "emotional ictuses" are distressing and perplexing to the patients experiencing them, most of these experiences being of a "primitive," "contentless" nature —"unexplainable after the bout is over," in the words of one patient.

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Case Material

In order to obtain a better understanding of the frequency and occurrence of these "emotional ictuses," we have reviewed, in the present study, the case histories of 744 seizure patients, all of whom had one or several electroencephalographic studies in one of our laboratories. We restricted our series to the age group between 6 and 70 years. In 388 subjects seizures could be classified as "symptomatic" epilepsy (i. e., with post-traumatic, atrophic, postinfectious, vascular, and/or expanding lesions as the presumed cause of epileptic discharges), whereas seizures in 354 patients were of unknown or doubtful etiology and were labeled "idiopathic." One hundred thirty-two subjects (34%) of the "symptomatic" group had temporal lobe seizures, either alone or in combination with other types of attacks, but all had temporal-lobe EEG foci. Only 71 patients (20%) of the "idiopathic" group had temporal lobe seizures. In order to obtain a more homogeneous series, we did *not* include the latter group in this report but limited our investigation to the "symptomatic" epilepsy patients only. Among the 132 subjects with temporal lobe seizures in the symptomatic group, 28 patients (21%) experienced "ictal emotions," approximately 7% of all patients being classified as having "symptomatic" epilepsy.

Williams [6] reviewed the case histories of 2,000 ambulant epileptic patients and encountered 165 subjects with "complex epilepsies." Of these, 65 were without any ictal emotional content, but emotions and moods ("which from their description form part of the epileptic disturbance") were encountered in 100 subjects. According to this author, the term "temporal lobe epilepsy" is a fairly accurate description concerning the lesions producing "complex epilepsies."

Type of Temporal Lobe Pathology Presumably Responsible for Ictal Emotions

The ages of our 28 subjects experiencing "ictal emotions" varied from 14 to 60, the median age being 33 years. The types of pathology thought to be responsible for temporal lobe seizures are tabulated in Table 1, in relation to the two most commonly observed "ictal emotions," i. e., "depression" and "fear." The majority of lesions were on an atrophic basis (15), apparently producing, more frequently, episodes of "ictal fear." This verified a previous observation which we first reported in May, 1955, before the American Psychiatric Association (Weil,[4] 1956), namely, that lesions affecting the temporal lobe cortex are particularly prone to produce "ictal fear." On the other hand, lesions which seem to activate the whole hippocampal-amygdaloid-temporal lobe complex, such as the postinfectious or cerebrovascular type, are more prone to produce depressive reactions. It is interesting to note that Williams,[6] in a lecture given in London in November, 1955, apparently came to the same conclusion: "Fear. . .occurred when the disturbance was in the outer as well as the other surfaces of the lobe. . . .When depression was felt, lesions were diffusely distributed in the temporal part of the brain."

TABLE 1.—*Ictal Emotions Associated with Temporal Lobe Pathology*
(28 Patients, Ages 14-60)

Pathology	No. of Patients	Ictal Depression	Ictal Fear
Atrophy, temporal lobe (including incisural sclerosis and post-traumatic gliosis)	15	6	9
Cerebrovascular lesions affecting temporal lobe(s) (thrombosis, embolus, hypertensive encephalopathy)	5	3	2
Postinfectious temporal lobe seizures	4	3	1
"Birth injuries" and congenital defects (involving temporal lobes)	2	1	1
Angioma, temporal lobe	2	1	1

Types of Ictal Emotions

In Table 2 are tabulated accessory ictal psychopathological phenomena in 14 subjects having *predominantly* "ictal fear" and in 14 other patients having *predominantly* "ictal depression." Indeed, "ictal depression" and

TABLE 2.—*Some Accessory Psychopathological Phenomena in Temporal Lobe Dysfunction*
(28 Patients, Ages 14-60)

	Predominantly Ictal Depression	Predominantly Ictal Fear	No. of Patients
Ictal depression	14	4	18
Ictal fear and panic	2	14	16
Visceral sensations	14	14	28
"Unreality experiences" and confusion (in the free interval)	5	7	12
Unpleasant olfactory sensations	9	0	9
Déjà vu experiences	4	3	7
Sudden rage	2	3	5
Paranoid interpretations	2	3	5
Unpleasant gustatory sensations	1	1	2

"ictal fear" are the most frequently observed emotions.

"Ictal depressions" are characterized by rather sudden let-down of mood and psychomotor retardation. They may assume all "shades" of melancholia, i. e., from simple listlessness and apathy to agitated depression with suicidal attempts.

"Ictal fears" are highly spontaneous, emotional events, the fear usually being of the "free-floating, undirected" variety and occasionally progressing to episodes of major panic.

These two emotional experiences occasionally overlap. (Four subjects with long depressive episodes also had brief periods of "fear and panic"; two patients with predominant experiences of "fear" also had "ictal depressions.") Both these emotional experiences are, from a psychopathological viewpoint, intimately related. However, there were certain neurological, electrophysiological, and phenomenological differences in patients displaying either predominantly "ictal depression" or predominantly "ictal fear" which seem to justify a separate grouping of patients experiencing these two "ictal emotions."

Comment on Certain Types of Ictal Emotions

Ictal Depressions.—Table 2 indicates that 9 out of our 14 subjects with "ictal depressions" also experienced olfactory hallucinations. This was in contradistinction to the patients with bouts of "ictal fear"; none of the latter group complained of "odor attacks," and only one of unpleasant gustatory sensations. Mulder and Daly [7] reported on 100 noninstitutionalized patients who had lesions of the temporal lobe and whose presenting complaints were usually thought to be psychiatric. Olfactory hallucinations occurred in a variety of these subjects; depressions, in 16 patients! Reviewing the statistics of Gibbs and Gibbs,[8] we noted that in their series of patients with "psychomotor" epilepsy, 1.5% had olfactory auras and 2.1% had depressive episodes. Among their subjects with anterior temporal foci, 1.1% had olfactory auras and 3.6% had depressions. However, only 0.3% of subjects having grand mal epilepsy experienced olfactory auras, and only 0.1% depressions. These percentages are small, but their relationship may be significant.

Stevens [9] also mentions the significant relationship of the temporal lobes, the olfactory brain, and emotional components of certain seizure patterns. The same author also states that "that disagreeable odor characteristic of the 'uncinate fit' never appeared as a first symptom of attack. . .and most commonly succeeded the subjective state of fear." This is not regularly so in our experience; we noted, indeed, uncinate attacks following bouts of depression, but other subjects experienced sudden olfactory hallucinations which *subsequently* seemed to trigger off prolonged depressive episodes. As a matter of fact, our experience coincides with the observations of Williams [6] regarding the prolonged nature of ictal depressions, in contradistinction to the much shorter bouts of ictal fear. This may be explained partially on the basis that fear attacks were frequently an aura manifestation prior to "full-blown" temporal lobe seizures and/or automatisms, whereas depressions tended to be expressions of subclinical "hippocampal-amygdaloid-temporal lobe epilepsy" or were occurring as after-discharges from the same structures following manifest seizure activation.

The interesting relationship between the rhinencephalon and certain emotional expressions has been experimentally demonstrated by Kaada et al.[10,11] in unanesthetized cats. MacLean [12] points out that the limbic system (great limbic lobe of Broca, including the hippocampus and its subcortical cell stations, i. e., the amygdala, septal nuclei, hypothalamus, anterior thalamic nuclei, etc.) is a common denominator of a variety of viscerosomatic *and* emotional reactions in all mammals. Indeed, each one of our subjects mentioned unpleasant visceral sensations in regular or periodic concomitance with ictal emotions. One patient states: "Tears come in my eyes when I get so despondent; it comes all the way from the pit of my stomach." The theory may be proposed that this region of the brain, so much concerned with the "experience and elaboration of emotions" (MacLean), may be "blocked" in its experience pattern by certain epileptic discharges (Weil,[5] 1956). This "blocking" led to such expressions in our patients as "emptiness," or "feelings don't reach me anymore," and may be subjectively translated as a "feeling of depression."

We observed in some patients almost "point-to-point" correlation of ictal depression with serial EEG recordings. Similarly, Ostow [13] (1953) observed in at least one subject moment-to-moment correlation between the affective significance of thoughts and electroencephalographic activity, taking advantage of a disturbance of the temporal lobe. This correlation, of course, is not universally true, nor does the electroencephalogram from the scalp always accurately portray abnormal electrical activity from inferior, and more mesial, temporal lobe strutures. It will also have to be pointed out that Jasper, Pertuisset, and Flanigan [14] originally stated that bilateral temporal-lobe EEG localization may be due to the localization of a *unilateral* epileptogenic lesion in the cortex, a theory which seems especially valid with "atrophic lesion of the uncus and hippocampal systems!" "Cross firing" to the *opposite* amygdala-hippocampus complex across the midline has been reproduced experimentally by Baldwin et al.[15] and by Faeth et al.[16] There is, therefore, no definite predictability that a unilateral temporal lesion will not produce a bilateral EEG disturbance, or even one on the contralateral side.

Figure 1 portrays serial EEG's during subclinical temporal lobe-uncinate seizures, associated with emotional depressions. In spite of clinical verifications of predominantly left temporal lobe atrophy, the hyperventilation EEG showed bitemporal activation.

A., a 39-year-old white man, a tavern owner (an abstainer himself!), had sustained a severe cerebral concussion at the age of 19. Two years afterward convulsions developed, occurring as often as two or three times a week. These were eventually controlled by diphenylhydantoin (Dilantin). One year later episodes occurred in which the patient found himself in "different" places, without knowing how he got there. "Yet, I felt here and there at the same time, a two-point feeling." He complained of perceiving foul odors, "like stuffed cabbage in a dirty outhouse." These "odor attacks" occurred during, or were usually followed by, severe emotional depressions, lasting from several minutes to 10 days. Family members suddenly appeared strange and unfamiliar; at other times he reported déjà vu experiences.

We examined this patient first in July, 1948, at which time his presenting complaints were "recurrent depressions" and "memory lapses." He had been seen in the past by a variety of medical practitioners and was apparently refractory to any form of standard psychiatric therapy, including ECT.

Subjective neurological signs were temporal headaches, associated with "occasional" double vision on left *and* right lateral gaze. Objective findings included a fine lateral nystagmus and accentuation of deep tendon reflexes on the right, particularly of the right upper extremity. Whereas findings on neuro-ophthalmological consultation and a left-sided arteriogram were normal, a pneumoencephalogram revealed an excessive amount of fluid, i. e., 205 cc., and some increase of subarachnoid air over the anterior and temporal areas, particularly on the left.

Serial EEG's were obtained over the years and showed good correlation of temporal-lobe EEG paroxysms, olfactory hallucinations, and depressions (Fig. 1). Olfactory attacks, as well as depressive episodes, could easily be activated by hyperventilation.

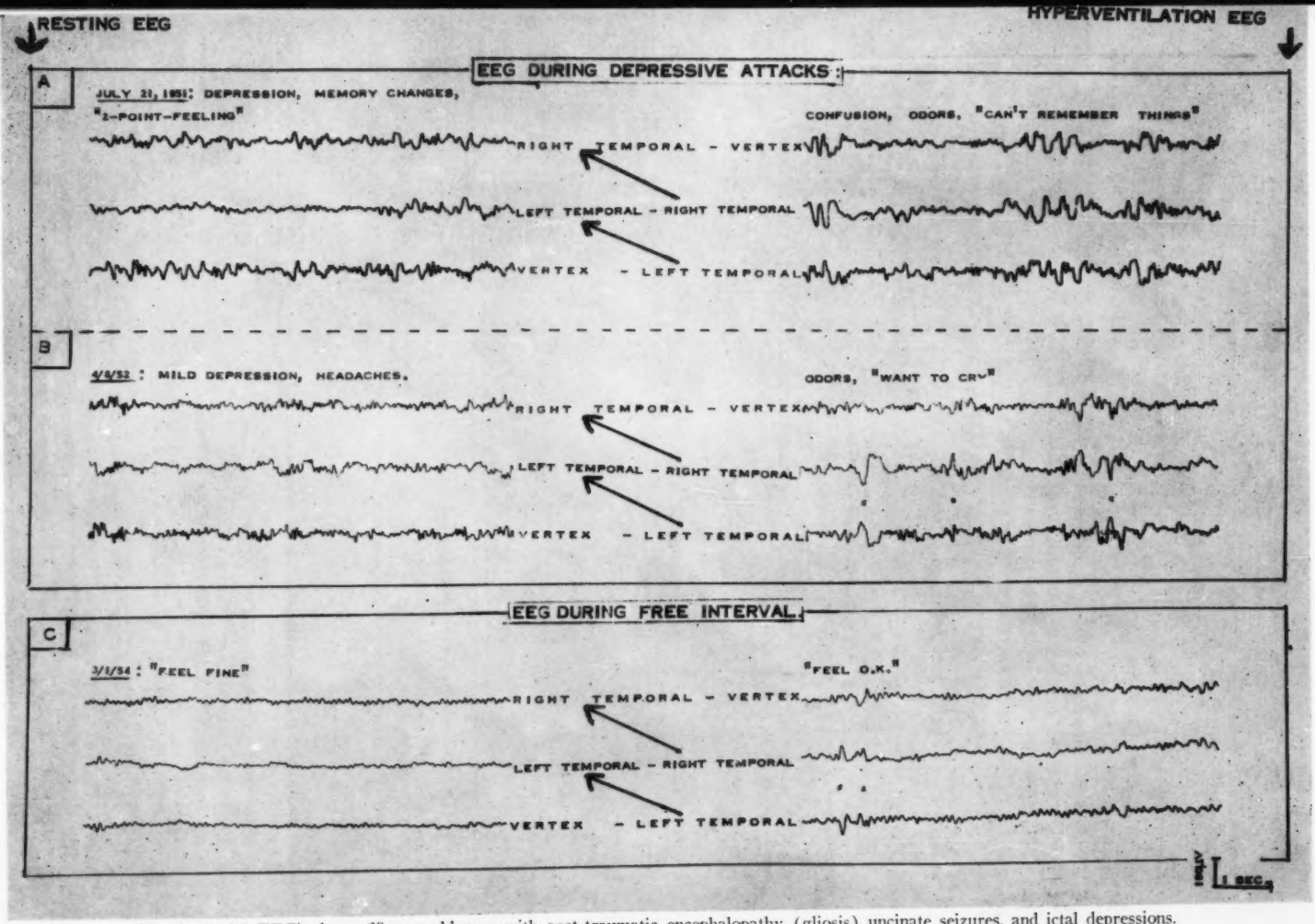


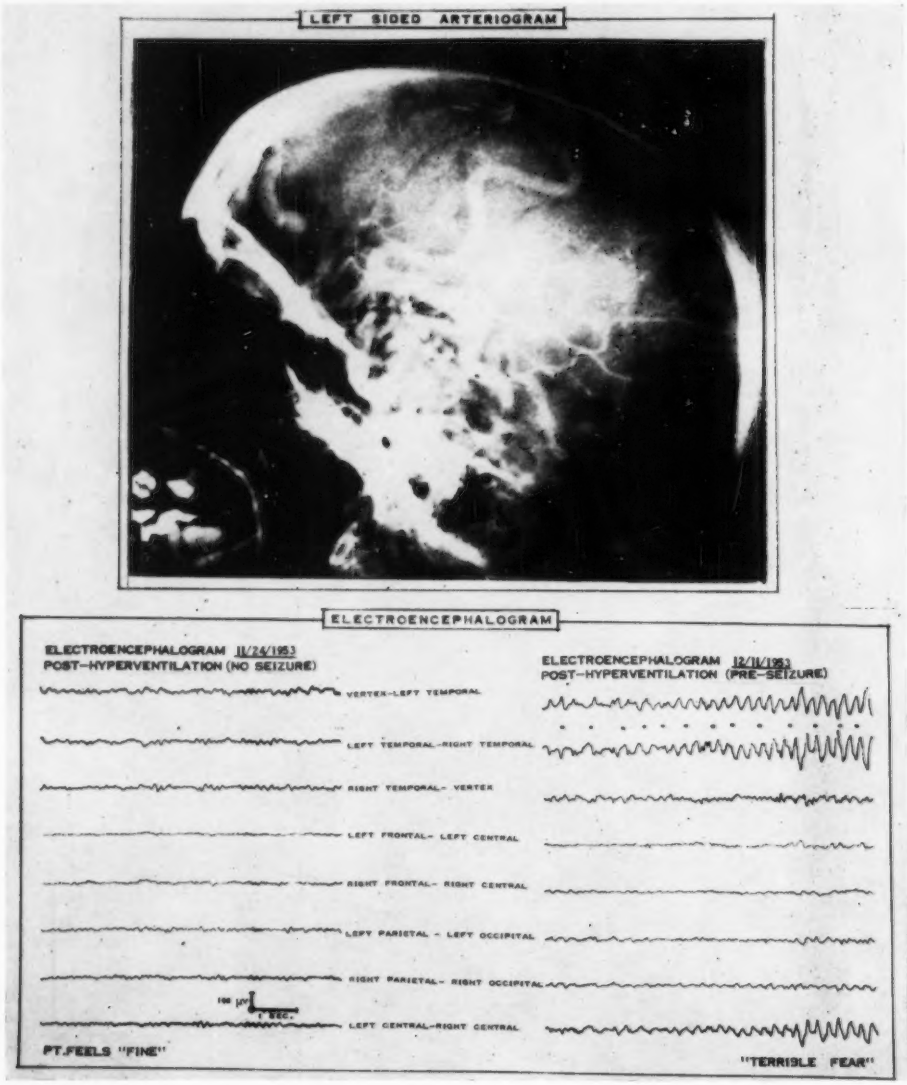
Fig. 1—Serial EEG's for a 39-year-old man with post-traumatic encephalopathy (gliosis), uncinate seizures, and ictal depressions.

A final diagnosis of "cerebral atrophy, with predominant involvement of left temporal lobe, post-traumatic," was made, and the patient was placed on an assortment of anticonvulsant medications. His depressions reach suicidal depth unless his medication is supplemented by dextro amphetamine U. S. P. Methamphetamine (Desoxyephedrine) given intravenously usually alleviated a depressive attack, as well as olfactory hallucinations.

There is one interesting postscript to A's history. His wife has sued him recently for divorce. This, the patient claims, "has produced a different sort of depression, one which I am able to handle and take care of . . . . It is only when I get the odors, memory lapses, and depressions that I become desperate."

Ictal Fear.—Ictal fear is usually a short-lasting phenomenon. The majority of our

Fig. 2.—Left-sided angioarteriogram and electroencephalogram for a 29-year-old woman, with angioma on the left temporal lobe, temporal lobe seizures, and episodes of ictal fear.



14 subjects experienced "fear and panic" during the temporal lobe aura, but sudden bouts of "undirected" fear occasionally were noticeable also during the "free interval." Figure 2 demonstrates electroencephalographic correlation of "ictal fear" with abnormal temporal lobe activity.

B., a 29-year-old housewife, developed "seizures" at the age of 17; the attacks originally only lasted a few seconds, were accompanied by a few dyskinetic movements, and were followed by a brief confusional state with automatisms. Her first and only grand mal attack occurred at the age of 22, during pregnancy. Eventually, she slowed down in her psychomotor output; her affect became labile, and she reported episodes of "strangeness and fear." "Fear attacks" frequently preceded minor seizures, and experiences of "strangeness" frequently followed. Her illness was diagnosed elsewhere as "hysteria" and "anxiety neurosis."

An initial neurological examination, in November, 1953, showed a predominantly sensory type of aphasia, difficulties in word finding, and a suggestive Babinski phenomenon on the right, even though patellar and Achilles reflexes were bilaterally absent.

An EEG study, performed on Nov. 24, 1953, was considered as still falling within normal limits (even during hyperventilation and posthyperventilation recording). At that time, the patient's anticonvulsant medication had not been discontinued, and she reported her subjective condition as "fine" (Fig. 2). However, a repeat EEG recording, on Dec. 11, 1953, following discontinuation of medication, produced in the posthyperventilation record left temporal focal slow spikes and delta waves (Fig. 2). Coinciding with the occurrence of this focal EEG abnormality, the patient expressed subjectively sensations of "anxiety" and "terrible fear." Upon being questioned, she could not explain these sensations. Following termination of the electroencephalographic recording, we witnessed a typical left temporal lobe seizure, with mastication movements, contralateral head turning, and confusion.

Arteriography revealed a very large racemose angioma, involving the entire left temporal lobe and a portion of the left frontal lobe (Fig. 2). Neurosurgical intervention (courtesy, Dr. William Nosik) was successful, and the temporal lobe seizures, as well as anxiety episodes, ceased.

Gibbs and Gibbs [8] noticed "fear" as an aura sign in 1% to 1.8% of their temporal-lobe-seizure patients. Gibbs, Fuster, and Gibbs [17] mentioned "fear" in 4 of a group of 300 patients with psychomotor epilepsy. Magnus et al.[18] described paroxysmal fear in 8 of 34 patients with masticatory seizures. According to these authors, masticatory seizures constitute a temporal lobe automatism, always being associated with disturbances of the sensorium. MacRae [20] reported 44 cases of epilepsy in which "fear without content and unrelated to thought processes or somatic sensations" was observed. The same author concluded in a previous paper [19] that the aura of fear has a focal significance, indicating abnormal physiological activity in the temporal lobe on either side. Gastaut [21] observed 300 psychomotor fits in human subjects and noted that "verbal automatisms sometimes express fright or anger." Stevens [9] feels that there is a definite "march" of temporal lobe epilepsy, progressing in the fear-flight-fight pattern. Williams [6] notes in his 61 subjects (among 100 cases of temporal lobe epilepsy) the close relationship between visceral activity and fear. It has been our experience that all 14 subjects with "ictal fear" had visceral sensations at one time or another. This, of course, again relates to the afore-mentioned "visceral brain" theory of MacLean.[12] Basically, then, "ictal fear" as an independent experience could be observed in our series as occurring under the following three main conditions: (*a*) as an isolated phenomenon, (*b*) as a phenomenon precipitated by or concomitantly occurring with abnormal visceral sensations, and (*c*) as a phenomenon associated with or concomitantly occurring with hallucinatory experiences and activation of memories; the latter, according to Penfield and Jasper,[3] are stored in the lateral and superior surfaces of the temporal lobes. These authors state: "One of the functions of the temporal lobes is to provide a storehouse of potential recollections. Another function is to play some role in the comparison of present experience with past experience." This latter statement may also bear a relation to the well-known "déjà vu experiences" observed with temporal lobe lesions. Four of our subjects with "ictal depressions" and three subjects with predominantly "ictal fear" also had concomitant déjà vu experiences.

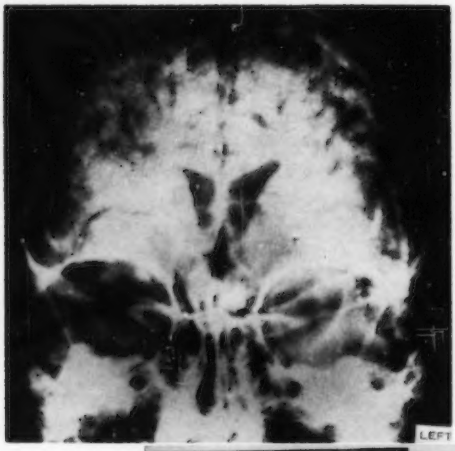
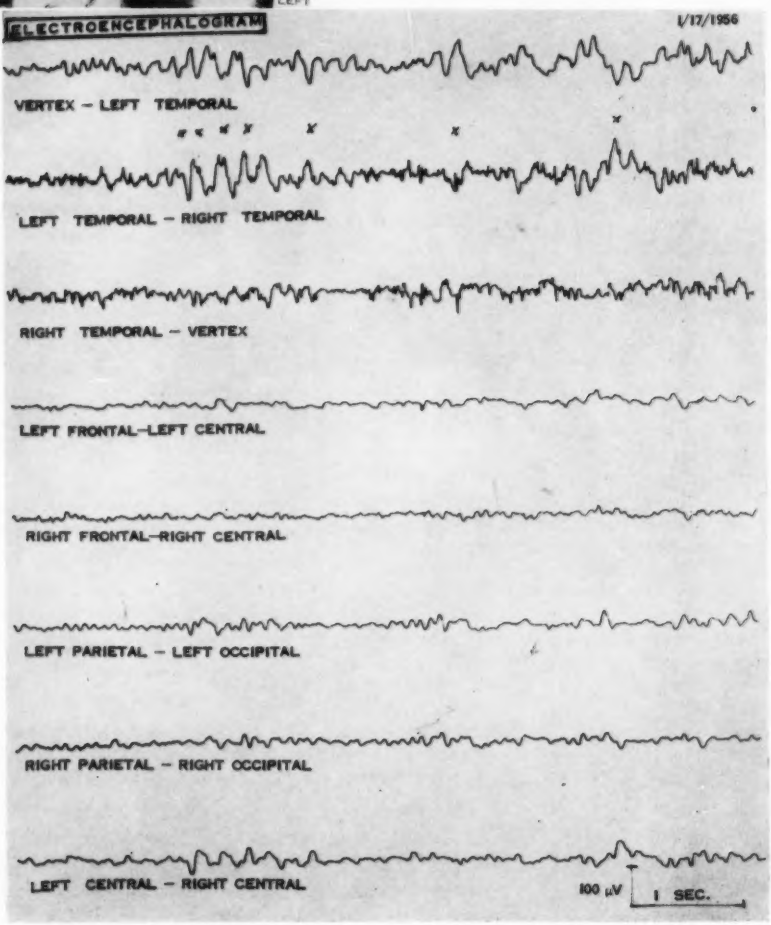


Fig. 3.—Pneumoencephalogram (Feb. 21, 1956) and electroencephalogram for a 19-year-old woman, having predominantly left-sided atrophy with temporal lobe seizures and rare grand mal attacks, associated with episodes of ictal fear and rage.



The correlation of ictal fear, memory activation, rage, visceral sensations, and abnormal temporal lobe activity is illustrated in the following case history (Fig. 3).

C., a 19-year-old salesgirl, developed bouts of "fear and fright" (which she could not explain properly) when she was only 6 years old. Following these episodes, she had brief "amnestic attacks" and complained "that the teachers confused her." After a minor head injury, at the age of 16, the patient experienced a prolonged episode of "being unable to remember things." Soon afterward her first grand mal convulsion occurred, which was ushered in by chewing movements and head turning to the right side. She was placed on diphenylhydantoin, but episodes of "fear and fright" occurred more frequently, usually followed by "memory lapses" and "automatic behavior." The patient located her fear "in her stomach." She reported having a "daydream" during these attacks which was always of the same content: Patient thought she was back in school and "scared."

Prior to her first consultation she had two additional grand mal seizures, antedated by temporal lobe prodromes. The parents complained, furthermore, that the girl had frequent rage reactions, with and without apparent stimulus, and that "her temper" was out of proportion to any actual emotional stimulus, when a stimulus did exist. The patient herself reported that her temper becomes worse when she is scared.

The neurological evaluation disclosed a very obese girl of 19. She had a slight abducens weakness on the left (associated with diplopia). There was some horizontal nystagmus on left lateral gaze. The protruded tongue deviated somewhat to the right. Deep tendon reflexes were accentuated on the right, particularly in the right upper extremity. The Hoffmann sign was positive on the right; Babinski and Chaddock signs were suggestive on the same side. A spinal fluid examination revealed normal dynamics, 1 cell per cubic millimeter, chemistry within normal limits, and colloidal gold curve 123332100. There was no definite laboratory evidence of hypothyroidism.

The EEG showed paroxysmally left-temporal theta activity (Fig. 3). A pneumoencephalogram (courtesy, Dr. William Nosik) showed characteristic dilatation of the left lateral ventricle, with some blunting of angles (Fig. 3). There were increased sulcus markings, more pronounced on the left side.

The final diagnosis was "incisural sclerosis, left temporal lobe."

Rage Reactions.—Rage reactions with minor or no obvious stimuli (as described in Patient C.) were noted in two patients with "ictal depressions" and in three subjects having predominantly "ictal fear." The occurrence of these phenomena is frequently perplexing, to the layman as well as to the physician. They may, indeed, denote a late stage in the fear-flight-fight pattern described by Stevens [9] during the sequential content analysis of a temporal-lobe-seizure "march." It is also postulated that the integration of incoming sensory stimuli with the motor-emotional output must be under some sort of regulating cerebral mechanism. This integrating system could be under control of limbic lobe components, this part of the brain being afferently related to all the sensory systems" (MacLean [12]). Loss of such integrating mechanisms may give rise to sudden "explosions" in the emotional sphere, i. e., rage reactions, as observed in our patients. Williams [6] encountered altogether 17 examples of ictal aggression in his already mentioned series, and "in all of them the lesion was in the anterior half of the temporal lobe or the inferior part of the frontal."

Experiences of Unreality and Confusion

Five subjects with predominant "ictal depression" complained of experiences of unreality and confusion; seven subjects with predominant "ictal fear" had similar experiences (Table 2). These experiences may be partially explained as due to slight dimming of the sensorium during clinical or subclinical temporal-lobe "firing." On the other hand, they may be subjective explanations by our patinets directed toward the experience of disturbed emotional functioning and "strange" olfactory and visceral sensations. Finally, the aforementioned disturbance of memory functions may also be subjectively "translated" by the patients as "experience of unreality and confusion."

Paranoid Interpretations

In psychologically predisposed subjects, we noted the occurrence of paranoid ideation accompanying visceral, olfactory, or depressive sensations. One subject thought

that her husband "had entertained some women with dirty feet," and opened all of the windows on a winter night. When interviewed a few days later, she stated that "some foul smell had confused her," apparently referring to an olfactory seizure associated with confusion of thought processes. Another patient, a man, who had, incidentally, been married five times, had ictal depressions with rage (verified by temporal-lobe EEG focus) and expressed, during these ictal depressions, ideas of unworthiness in psychosocial and psychosexual directions. During these episodes he suspected his past spouses, as well as his present one, of "taking up with other men." These bouts were short-lived but universally associated with confusion of thoughts. After these episodes and after clearance of his sensorium, the patient was most ashamed of his previously expressed accusations and was unable to furnish any proper explanation of them. It is quite obvious that experiences like these may lead to consultation with a psychiatrist rather than to one with a neurologist!

Pleasurable Experiences

Penfield and Jasper[3] state that "so far as our experience goes, neither localized epileptic discharge nor electrical stimulation is capable of awakening any such sensation." This corresponds with the experiences of our group of patients, none of whom had any "pleasurable" ictal emotional sensations. We reported recently epileptic laughing fits in four epileptic subjects (Weil,[22] 1957), which were, however, predominantly motor phenomena and not accompanied by any "ictal euphoria." A review of the literature on "laughing fits," as well as our own observations (Weil,[22] 1957), makes it apparent that such seizures are prone to occur in disturbances around third-ventricle areas and the diencephalon, with subsequent electrophysiological spread to one or both temporal lobes.

However, Williams,[6] among 2,000 epileptic subjects studied, mentions 9 patients who had "pleasant feelings" during temporal lobe discharges. This author argues that in such cases a spread of the epileptic discharge to the frontotemporal regions must have occurred. Stevens,[9] among her series of 40 patients with temporal lobe seizures, mentions 3 who experienced sensations of pleasure, but these subjects had a "cephalic" aura, free of fear components. Should such pleasurable sensations really occur during temporal lobe discharges, they must certainly be the exception as compared with the large variety of unpleasurable sensations usually experienced.

We tend, rather, to agree with the observation by Ostow[23] (1957) that the "psychic function of the temporal lobe is the formation of apperceptive judgments, especially negative ones."

Summary

We encountered among 388 subjects with "symptomatic" epilepsy (i. e., with posttraumatic, atrophic, postinfectious, vascular and/or expanding lesions as the presumed cause of epileptic discharge) 132 patients with clinical and electroencephalographic evidence of temporal lobe epilepsy. In this group, 28 subjects experienced "ictal emotions" (7% of all our subjects classified as "symptomatic epilepsy" and 21% of the patients with temporal lobe discharges).

The majority of lesions were thought to be on an atrophic basis (15 patients). Other types of temporal lobe pathology included cerebrovascular lesions (5 cases), postinfectious pathology (4 cases), angioma of the temporal lobe, (2 cases), and "birth injuries" (2 cases).

Fourteen subjects had predominantly ictal depressions; 14 other subjects, predominantly ictal fear. Whereas ictal emotions generally were experienced during the aura as an expression of epileptic afterdischarges, or even during the "seizure-free interval," the occurrence of ictal fear was more frequently observed during an aura. "Ictal fear" was usually of shorter duration than "ictal depression," the latter being ex-

perienced more frequently during the "free interval" between manifest seizures or as an isolated expression of an epileptic after-discharge.

Ictal fear was frequently associated with *cortical* temporal lobe pathology (both anatomically and electrographically), whereas depression was more frequently associated with diffuse temporal lobe lesions. Prolonged depressions were frequently associated with olfactory hallucinations.

In some cases a moment-to-moment correlation between the experience of ictal emotions and the occurrence of temporal-lobe EEG abnormalities could be established.

Accessory psychopathological phenomena in temporal lobe dysfunction, such as visceral sensations, unreality experiences, déjà vu experiences, sudden rage reactions, and paranoid interpretations, were briefly investigated from a viewpoint of phenomenological observation and psychoneurological correlation.

The absence of any "pleasurable ictal sensations" in our series is noted.

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Hypertensive Fibrinoid Arteritis of the Brain and Gross Cerebral Hemorrhage

A Form of "Hyalinosis"

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Stroke, apoplexy, and cerebral vascular accident are clinical terms applied to the situation resulting from a sudden major injury to the brain due to disease of the cerebral blood vessels and/or alteration of the cerebral circulation. Pathologically, the cerebral lesion in such circumstances is an infarct or a hemorrhage. The infarct, an area of necrosis due to ischemia, may be associated with a varying degree of hemorrhage in the form of isolated or confluent petechiae, and this hemorrhage may be minimal, moderate, or severe in degree. Even when the extravasation of blood into an infarct is severe, such hemorrhagic infarct should be distinguished fundamentally from a cerebral hemorrhage. The latter is characterized by a gross extravasation of blood into the cerebral tissues without obvious necrosis, except at the periphery of the hemorrhage, where the necrosis may be secondary to compression of the tissues or of the associated vessels. The separate identity of these two processes is not universally conceded. Some have stated that the gross hemorrhage is the result of an antecedent infarct. Both infarcts and hemorrhages are frequently associated with arteriosclerosis and hypertension, and they may occur together in the same brain.

This paper will deal with the gross cerebral hemorrhage specifically associated with hypertension, and will not be primarily concerned with hemorrhagic infarcts or with the cerebral hemorrhages that are the result of trauma, blood dyscrasia, the administration of anticoagulants, sepsis, or the rupture of "congenital" aneurysms or angiomatous malformations. In patients with hypertension vascular changes which may result in rupture and gross hemorrhage are observed. These changes have been described previously, often under the term hyalinosis, a term that appears to include other types of change as well, so that the relationship of the arterial changes to hypertension and cerebral hemorrhage has been partially obscured. The fibrinoid form of hyalinosis, that specifically related to hypertensive hemorrhage, may be distinguished by special staining procedures.

Observations

The vascular changes which concern this paper were present only in the brain. They consisted essentially of a fibrinoid alteration of the vessel wall associated with inflammation and the extravasation of blood. The term fibrinoid is used descriptively for materials which resemble fibrin tinctorially with hematoxylin and eosin, azocarmine, and phosphotungstic acid hematoxylin stains. The involved vessels were generally small arteries, ranging from 0.2 to 0.8 mm. in diameter, oftener intraparenchymal than

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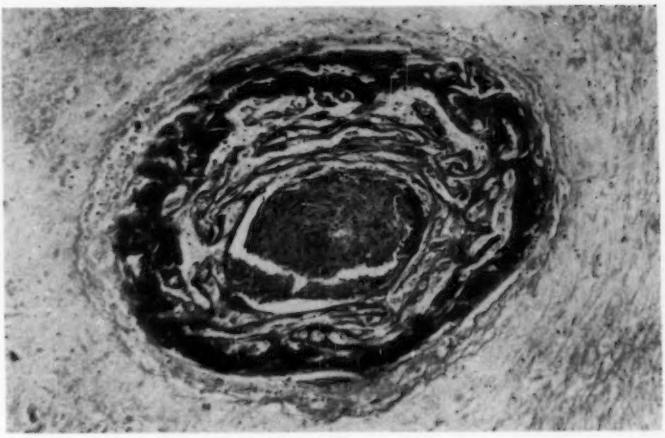

Fig. 1.—Cerebral artery showing irregular deposits of fibrinoid materials in the wall. These materials were stained red. Azocarmine stain; reduced to 61% of mag. × 230.

subarachnoid in location and more frequently within the basal ganglia than the cerebral cortex, cerebellum, or brain stem. Rarely, the wall of a vein was similarly affected. The fibrinoid alteration affected either the entire circumference of a vessel at a given level (Fig. 1) or only a part of the circumference (Fig. 2). In the latter circumstance, there was occasionally a focal aneurysmal dilatation of the vessel wall at that point (Figs. 3 and 4). The fibrinoid change involved only a small segment of the length of a vessel, and sometimes involved a cluster of adjacent vessels. The change most frequently affected the entire thickness of the vessel wall, but in other instances it was seen at times to involve the intima, the elastic lamella, the media, or the adventitia to the exclusion of other portions of the wall. It is clear that the early stages of this change involved any one of these sites to the transient exclusion of the remainder of the wall. The fibrinoid materials were smudgy, hyaline, or fibrillar, and usually intensely

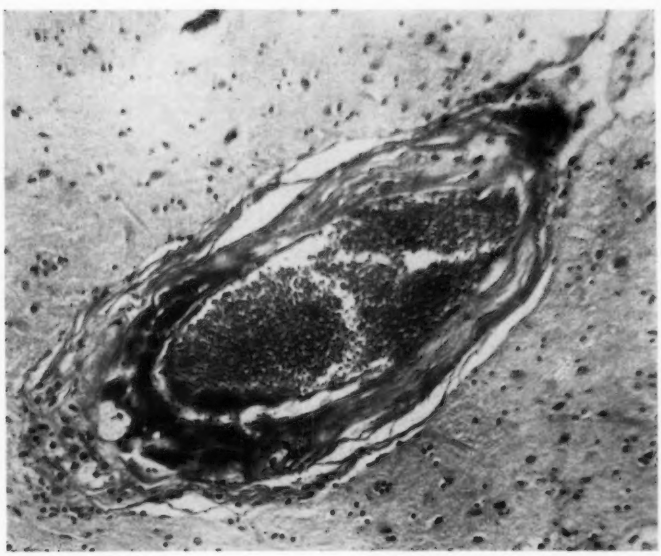

Fig. 2.—Cerebral artery showing focal fibrinoid alteration. Hematoxylin and eosin; reduced to 75% of mag. × 200.

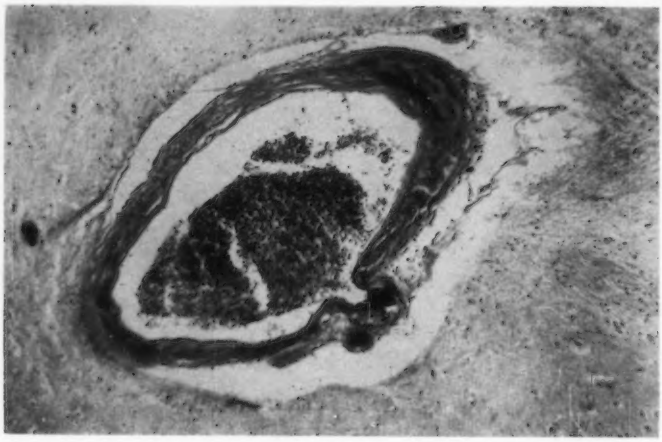

Fig. 3.—Cerebral artery showing fibrinoid alteration of wall at site of branching or aneurysmal outpocketing. The fibrinoid materials were stained red; the remainder of the wall was stained blue. Azocarmine stain; reduced to 61% of mag. × 170.

eosinophilic when stained with hematoxylin and eosin; but occasionally they disclosed a distinct purple tint. The fibrinoid materials consistently stained red with the azocarmine method, blue with the phosphotungstic acid hematoxylin technique, and yellow with the Van Gieson method.

In some of the brains in which these fibrinoid alterations were observed, there were vessels which resembled those showing the fibrinoid change when stained with hematoxylin and eosin, but differed from them by appearing blue with the azocarmine method, tan with the phosphotungstic acid hematoxylin technique, and yellow or red with the Van Gieson stain. These staining characteristics more closely resemble those demonstrated by collagen than fibrin or fibrinoid, and may be designated as hyalin of the collagen type for purposes of identification. In many such instances the walls of these vessels were very markedly thickened and the lumens considerably narrowed (Fig. 5). In some instances the lumen was obliterated by a thrombus or by dense fibrous connective tissue (Figs. 4 and 6).

These changes, particularly the fibrinoid, were often associated with inflammation and the extravasation of blood. In a few cases the inflammation was acute (Figs. 7 and 8), characterized by a polymorphonuclear leukocytic infiltrate and the presence of nuclear

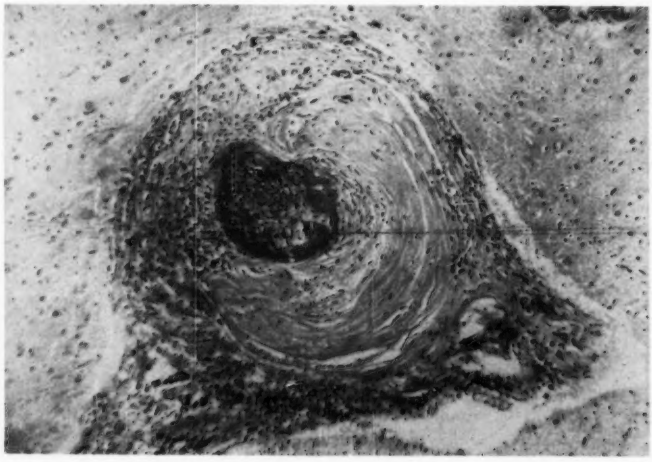

Fig. 4.—Cerebral artery showing focal defect in dense fibrotic wall. The lumen is occluded by a thrombus. There is a severe infiltration of the surrounding tissues by chronic inflammatory cells and phagocytes filled with blood pigments. Hematoxylin and eosin; reduced to 63% of mag. × 190.

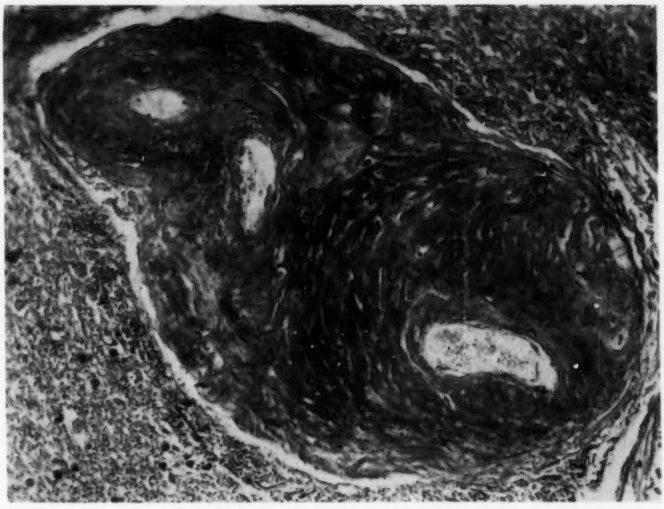

Fig. 5.—Cerebral artery showing marked fibrotic thickening of the wall and narrowing of the lumen. The entire wall stained blue. Azocarmine stain; reduced to 61% of mag. × 310.

debris. More frequently the inflammatory infiltrate consisted essentially of lymphocytes, large mononuclear cells, and some fibroblasts (Figs. 4, 6 and 7). Rarely, a plasma cell, polymorphonuclear eosinophilic leukocyte, or multinucleated giant cell of the foreign-body type was observed. This chronic inflammatory infiltrate was sometimes very severe and was present within the wall of the vessel and in the perivascular area. At times the perivascular astrocytes were hypertrophied. Many of the mononuclear cells contained blood pigments in their cytoplasm, and such pigments were also present in considerable quantities extracellularly in the perivascular tissues (Figs. 4 and 6). This vascular change was not infrequently associated with the presence of small, focal, old infarcts in the neighboring tissues. These very frequently contained appreciable quantities of blood pigments.

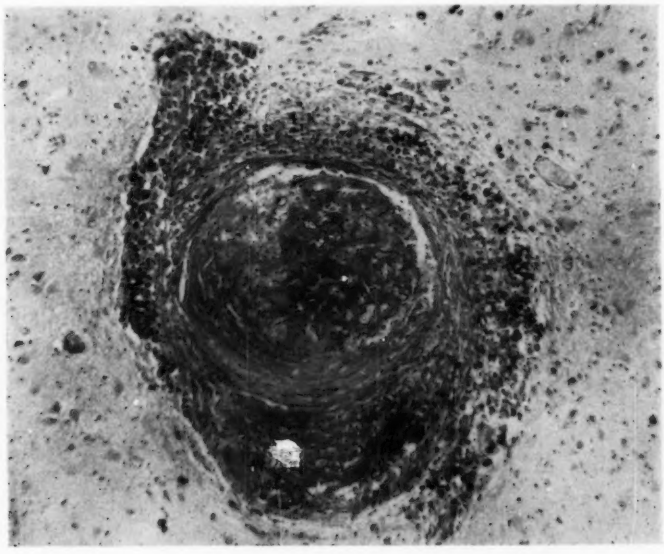

Fig. 6.—Cerebral artery showing large quantities of blood pigments, free and within phagocytes, in the surrounding tissues. The lumen is occluded by an organized thrombus. Hematoxylin and eosin; reduced to 75% of mag. × 140.

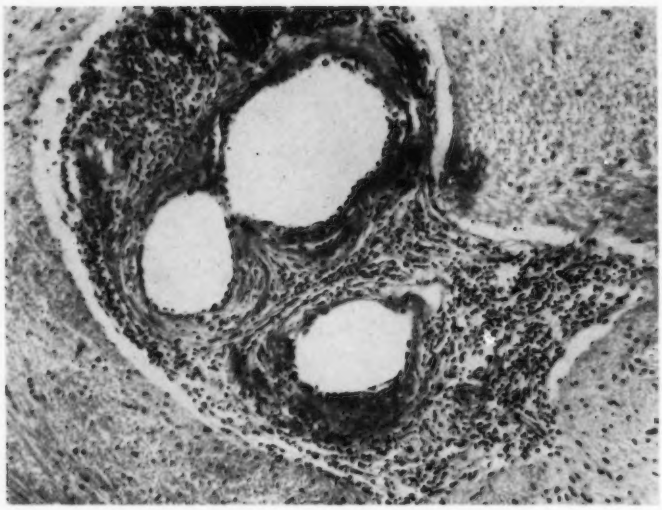

Fig. 7.—Cerebral arteries showing acute necrotizing fibrinoid changes in lower portion of lower vessel, with more chronic fibrinoid changes in other vessels. There is a severe chronic inflammatory infiltrate in the surrounding tissues, as well as some pigment containing phagocytes. The upper portion of the upper vessel contains mineral deposits in the wall. Hematoxylin and eosin; reduced to 61% of mag. × 160.

Vessels with the alterations described were found in small numbers only after intensive histologic search, requiring up to 24 paraffin blocks. These vascular changes were associated with hypertension and with the gross cerebral hemorrhage related to hypertension. Hypertension was present in all of the 22 cases in which this arterial lesion was observed (Table), as indicated by a clinical history of hypertension, the presence of hypertension on physical examination, the observations at autopsy of a significant cardiac hypertrophy in the absence of valvular disease, and/or changes in the kidney and other organs indicative of arteriolar sclerosis.

In 18 of the 22 patients, abnormally elevated systolic and diastolic blood pressures were observed during their clinic visits and/or hospitalization. Three of the others gave a clear history of hypertension for many years, although this was not directly observed in the clinic or ward. In one of these (Case 18), an 86-year-old woman, the maximal recorded blood pressure was 190 mm. Hg systolic and 70 mm. Hg di-

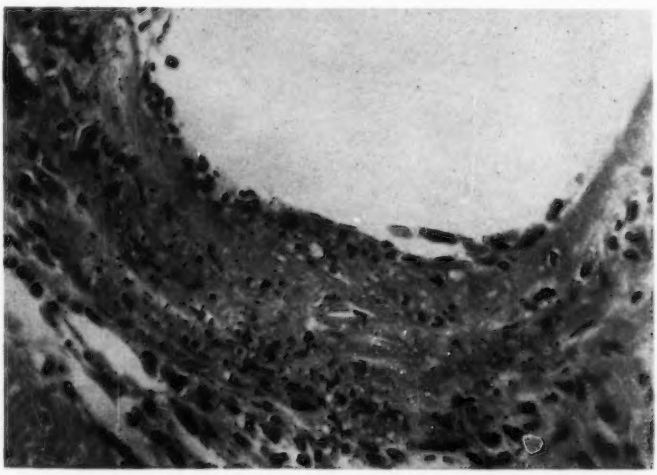

Fig. 8.—Acute necrotizing fibrinoid changes in wall of cerebral vessel. This is the same vessel as that shown in the lower portion of Figure 7. Hematoxylin and eosin; reduced to 63% of mag. × 500.

Hypertension and Fibrinoid Arteritis *

Case	Sex	Age, Yr.	Blood Pressure, Mm. Hg		Duration of Hypertension (Yr.)	Weight of Heart, Gm.	Neuropathological Findings	Additional Data
			Systolic	Diastolic				
1	M	60	180-270	100-110	¼		FH, R	
2	M	58	180-230	100-130		410	FH	N
3	M	51	200	110	15	790	FH	N, F
4	M	65	240	130		550	FH, R, OI	N, FMI, OMI
5	M	54	180-240	100-140		320	OH, OI	N, P
6	M	66	215-240	105-130	5	430	FH, OH	N
7	M	71	180-200	90-100	Many	500	OH, OI	N
8	M	55	250-260	120-160	Many	940	OH	N, F, "MH"
9	M	76	190-200	108-120	1	470	FH, OH	N, P, FMI
10	M	70	190	90		490	FH, OH	N
11	M	67	190	130	Many	520	FH, R	N, F
12	M	65	200-260	140-160	Many	580	FH, FI, DI	N, D
13	M	73	200	50	Many	740		N, RHD
14	M	63	130-195	80-110	12	210	OH, OI	N
15	F	72	180	120		310	FH, R	N, A
16	F	68	160	100		520	OH, OI	N
17	F	46	240-260	140-160	Many	380	OI	N, "MH"
18	F	86	120-190	60-70	Many	300	OI	N
19	F	72	120-150	60-80	Many	375	OI	N, P, OMI
20	F	70	120-190	60-120	25	720	OI	N
21	F	77	220	110-120	Many	500	OI	N, T
22	F	77	170-220	80-220		450	M	N

Under "neuropathological findings," FH designates the presence of a fresh gross hemorrhage; OH, a hemorrhage believed to be more than one month old; R, the rupture of a fresh hemorrhage into the ventricular system; FI, a fresh cerebral infarct; OI, an old cerebral infarct, more than two months old; M, an incidental meningioma. There were no lesions in the brain of Case 13 other than the arteritic.

Under "additional data," N, indicates the presence of arteriolar nephrosclerosis; F, hemorrhages and exudates in the ocular fundi; FMI, a fresh myocardial infarct; OMI, an old myocardial infarct; P, chronic pyelonephritis; "MH," clinically accelerated "malignant" hypertension; D, diabetes mellitus; RHD, rheumatic heart disease with aortic insufficiency; A, an unruptured saccular aneurysm, and T, thrombosis of origin of left vertebral artery.

In Case 1, the autopsy was limited to examination of the brain.

astolic. She weighed 110 lb. and was 49 in. in height. Her heart weighed 300 gm., and was considered hypertrophied for her stature. Her kidneys revealed arteriolar nephrosclerosis. In another (Case 19), a 72-year-old woman, the maximally observed blood pressure was 150 mm. Hg systolic and 80 mm. Hg diastolic. Her heart weighed 375 gm., and arteriolar changes were also present in her kidneys. There was a healed myocardial infarct, which may have accounted for the normal blood pressure levels during her terminal illness. The third case (Case 13), was that of a 73-year-old man with aortic insufficiency due to rheumatic heart disease. The blood pressure readings were 200 mm. Hg systolic and 50 mm. Hg diastolic. The heart weighed 740 gm., and arteriolar nephrosclerosis was present. In Case 10, a man 70 years old, the only recorded blood pressure reading was 190 mm. Hg systolic and 90 mm. Hg diastolic. His heart weighed 490 gm., and arteriolar changes were present in the kidneys.

In 11 of the 13 men on whom complete autopsy data were available, the heart weighed between 410 and 940 gm. In Case 14 the heart weighed 210 gm. This patient was 63 years old, weighed 90 lb. at death, and was 65 in. tall. Blood pressure readings as high as 195 mm. Hg systolic and 110 mm. Hg diastolic were recorded during his 12-year hospitalization. In Case 5 the heart weighed 320 gm. This patient was 54 years old, weighed 90 lb. at death, and was 67 in. tall. Blood pressure readings as high as 240 mm. Hg systolic and 140 mm. Hg diastolic were recorded. In six of the eight women the heart weighed between 375 and 720 gm. Case 18 has already been discussed. In Case 15 the heart weighed 310 gm. The patient was 72 years old, weighed 130 lb. at death, and was 61 in. tall. Blood pressure readings as high as 180 mm. Hg systolic and 120 mm. Hg diastolic were recorded.

Of the 21 patients in whom autopsy included the visceral organs, arteriolar sclerosis of moderate or severe degree was noted in all; and this involved the kidney and other organs, such as the pancreas and adrenals. Necrotizing arteriolar lesions in these organs were not observed, not even in the two instances in which the hypertension was considered clinically "malignant." Chronic pyelonephritis was present in three instances, and this may have played a role in the causation of the hypertension. Glomerulonephritis was not observed. In one patient, seen in consultation, not included in this series, a pheochromocytoma, as well as arteriolar changes, was noted. In all of the patients, fibrinoid arterial lesions were seen only in the brain, and not in any of the other organs examined.

In addition to the fibrinoid arteritis in the brain in all 22 cases, a gross hemorrhage was present in 15. This was fresh in seven cases, old in five cases, and in three others both fresh and old hemorrhages coexisted. Four of the fresh hemorrhages had ruptured into the ventricles. In seven cases there was no evidence of hemorrhage. In two instances fibrinoid arteritic lesions were found in the marginal tissues about the hemorrhage (Fig. 9). In other cases the arteritic lesions were observed elsewhere in the brain, often in the basal ganglia contralateral to the hemorrhage, occasionally in the pons, and occasionally in other tissues. In 11 instances infarcts were also present in the brain.

There were 14 men and 8 women in this series, a difference not considered significant. Their ages ranged from 46 to 86 years; the average age of these patinets was 66.5 years.

This cerebral arteritis was not found in the brains of the 16 other patients with hypertensive cerebral hemorrhage encountered during the same period of time, although these were studied with equal intensity. No vascular lesions of the types described were observed in the brains of normotensive persons.

Comment

The large number of pathogenic mechanisms suggested to explain the gross cere-

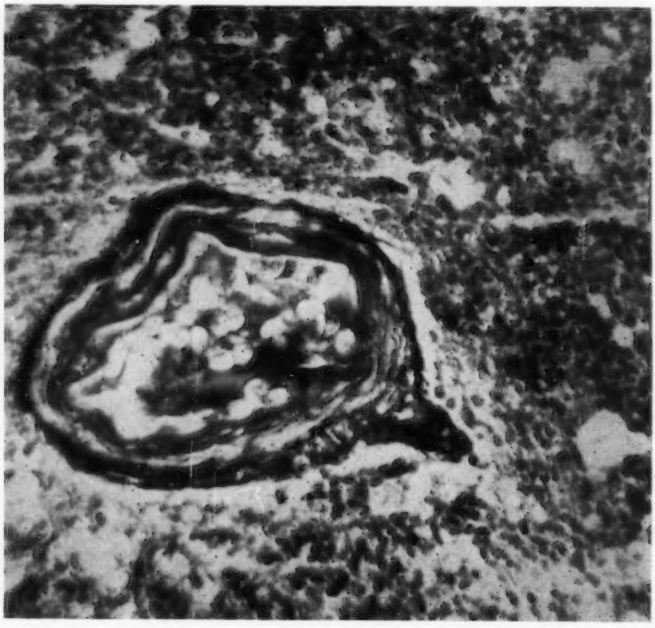

Fig. 9.—Fibrinoid alteration of cerebral artery at margin of fresh hemorrhage. The fibrinoid materials in the inner portion of the wall were stained red; the outer adventitia was stained blue. Azocarmine stain; reduced to 92% of mag. × 500.

bral hemorrhage of hypertensive persons attests to the lack of unequivocally convincing evidence for any one of them.[1,2] Such suggestions include spasm[3]; the destruction of the tissues surrounding an artery,[4] although this may not decrease their support[5]; venous lesions[6]; miliary[7] or dissecting[8] aneurysms, though these may have been misinterpreted,[9,10] and arteriosclerosis,[11,12] although some lesions designated as arteriosclerotic have been otherwise interpreted.[13]

In the light of our own observations, we are most impressed with those reports describing changes in the cerebral arteries variously characterized as arterial necrosis or angionecrosis,[3,14-17] or as hyalinosis or hyaline degeneration.[13,18-20] As is true with respect to aneurysm formation, some difficulty exists in distinguishing between those necrotizing arterial lesions which result directly or indirectly from a gross hemorrhage and those necrotizing arterial lesions which conceivably could be the cause of the hemorrhage. Thus, arterial lesions like those noted in brains with traumatic hemorrhage[21] are less likely to be significant.

The concept of hyalinosis in cerebral arteries is a frequently recurring theme in the neuropathological literature. In an extensive review, Scholz and Nieto[13] concluded that this process was not related to either cerebral infarction or cerebral hemorrhage, although earlier[3,12,17,21] and later[14-16,18,19] reports on what is presumably the same process would clearly implicate this lesion in the causation of cerebral hemorrhage. As might be expected, the various observers differ somewhat in terminology, in the details of their descriptions of the arterial lesions, in the limits of what they would include in an entity, and in the pathogenic mechanisms postulated. In general, hyalinosis is characterized by the deposition of eosinophilic materials in the intima or in other portions of the walls of arterioles and small arteries, and these materials are usually stained yellow by the Van Gieson method and are stained by Sudan stains for lipids.

The arterial changes described in this paper are similar and fall into the group designated as hyalinosis. However, we should prefer to separate vessels showing hyalinosis into two groups on the basis of the tinctorial properties of the hyaline materials, particularly with the Mallory stains. We prefer the azocarmine and phosphotungstic acid hematoxylin stains, but the results with the other Mallory stains are equally significant. In one group of vessels showing hyaline changes, the materials within the vessel walls stain red with the azocarmine stain, blue with the phosphotungstic acid hematoxylin method, yellow with the Van Gieson technique, and bright red or slightly purple with hematoxylin and eosin. Since fibrin stains in a similar fashion, we should like to designate these materials as fibrinoid forms of hyaline. It is these fibrinoid forms which we believe to be most specifically related to hypertensive hemorrhage. Materials with similar tinctorial properties are occasionally observed in the small renal arterioles in "malignant" hypertension, in some renal vessels in diabetic intercapillary glomerulosclerosis,[22] in the walls of arteries in periarteritis nodosa, and in some of the experimental conditions discussed below. Such fibrinoid materials are almost certainly heterogeneous in character and resemble, but are not identical with, fibrin and each other.[23] They have been thought to represent glycoprotein,[24] fibrinogen,[25] necrotic smooth muscle,[26] or necrotic collagen or ground substance.[27] The presence of such materials is generally considered to indicate damage to the vessel wall, often severe; and this is certainly true in instances in which one observes, in addition, nuclear debris, an inflammatory reaction, or permeation with blood, suggesting that necrosis of the vessel wall may have occurred.

The designation of these materials as fibrinoid forms of hyalin serves to distinguish these from another group of hyaline materials which tinctorially resemble collagen

and may represent types of collagen, and which we should like to designate descriptively as the collagen forms of hyalin. These latter materials are sometimes less deeply eosinophilic than fibrinoid, are tan with phosphotungstic acid hematoxylin and blue or green with the other Mallory stains, and stain yellow, orange, or red with the Van Gieson method. Materials of this type are found frequently in small splenic arterioles, in the renal arterioles in nondiabetic patients with "benign" hypertension, in some such vessels in diabetics with hypertension,[22] and in portions of the walls of arteries previously damaged by arteriosclerosis and in the healed stage of other destructive processes, including periarteritis nodosa and experimental necrotizing arteritis.

We should have preferred to use the words "fibrinoid" and "hyalin" for the fibrinoid forms of hyalin and the collagenous forms of hyalin respectively; but, unfortunately, usage has rendered these terms most confusing. Montgomery and Muirhead[28] designated as vascular hyalin, materials which stain red with Mallory's and Masson's stains and which might be considered as falling into the fibrinoid group. Indeed, they concluded that vascular hyalin and vascular fibrinoid are indentical. On the other hand, Altshuler and Angevine[29] used the term fibrinoid to describe materials, some of which stained red with the Van Gieson method and yellow-orange (tan) with phosphotungstic acid hematoxylin. In our experience, materials staining in this fashion would stain blue with the azocarmine method. These tinctorial properties are characteristic of the collagen form of hyalin. In the neuropathological literature the term hyalinosis has been used apparently for both forms of arterial change.

In the light of the heterogeneous character of the fibrinoid materials, and probably of the other hyaline materials as well, it is probable that the distinction between the two classes of hyaline substances outlined above is an oversimplification. If, as we believe, the fibrinoid materials may heal by fibrous replacement and hyalinization of the collagen type, it is apparent that there will be intermediate stages in which materials of the two types coexist and the staining reactions will be mixed. It is also possible that some fibrinoid materials may be of such nature that they stain as outlined in some respects but not in others. In the brain, however, the distinction between the two forms of hyaline changes is clear, and is consistently demonstrated with the azocarmine and phosphotungstic acid hematoxylin stains, much less consistently with the Van Gieson stains. With these stains the fibrinoid materials stain red, blue, and yellow, respectively, while the collagen form of hyalin is characterized by blue, tan, and red or yellow staining properties, respectively. Both forms of hyalin stain red with hematoxylin and eosin, so that the mineral deposits so often noted in the walls of vessels in the globus pallidus and elsewhere, which stain blue with hematoxylin and eosin, are readily distinguished, although they resemble fibrin with the Mallory stains.

In the brain, the fibrinoid type of arteritis is observed most commonly in hypertensive persons. It is true that arteries lying within a zone of acute tissue necrosis, as in an infarct, may themselves become necrotic and contain such fibrinoid materials, probably fibrin itself, within their walls. Fibrinoid changes may be observed also in rare instances in which the cerebral arteries are involved in granulomatous angiitis or generalized periarteritis nodosa, and possibly in other circumstances. In most instances, however, such fibrinoid changes are observed in the cerebral vessels of hypertensive persons, are often associated with inflammatory changes and evidence of blood extravasation, as described above, and sometimes are associated with gross cerebral hemorrhage. The presence of fibrinoid with an inflammatory reaction denotes a marked weakness of the vessel wall, and this would be confirmed in those instances in which the extravasation of blood is indicated by blood pigments in the surrounding tissues or by

gross hemorrhage. Hypertension may be a factor not only in inducing the fibrinoid change but in favoring rupture once this change had occurred.

Occasionally, the cerebral arteries of hypertensive patients reveal a very marked fibrotic thickening of the wall with partial or complete hyalinization of the collagen type, a marked narrowing or obliteration of the lumen, and, often, a chronic inflammatory infiltrate and/or blood pigments in the walls and in the surrounding tissues. In this instance, we would stress the associated inflammatory changes and the evidence of blood extravasation, since hyalinization of the collagen type without these features is observed in normotensive persons. It will be recalled that these features are frequently present with the fibrinoid alteration, and that hyaline changes of both types may coexist in the same brain, and, indeed, in the same vessel. We suggest that the fibrinoid form of hyalin may be transformed into the collagen form of hyalin as part of a healing process. The marked narrowing of such vessels, and of many with the fibrinoid alteration, would be expected to lead to local tissue ischemia. Small, focal, old infarcts are often observed in the tissues about these vessels, and these tend to contain larger quantities of blood pigment than infarcts in normotensive persons. The basic hypertensive arteriopathy may, therefore, injure the brain by inducing hemorrhage when fresh and small focal infarcts when older.

Hyaline changes of the collagen type without associated inflammation or bleeding are observed in the cerebral arteries of normotensive, as well as hypertensive, persons. In the latter, such hyaline changes may take the form just described, possibly with complete subsidence of the inflammation, or may result in a uniform thickening of the walls of small arterioles without associated inflammation. Unlike the situation prevailing in the kidney, this latter change, arteriolar sclerosis, is found in the brain in a minority of hypertensive patients. In normotensive persons, hyaline changes in the walls of arteries and arterioles are found within lesions of varied character, as in glial scars, areas of tract degeneration, and the common adhesions of the lateral ventricles. The occurrence of hyaline changes in such circumstances has served to minimize the significance of hyalinosis as a cause of cerebral hemorrhage or of infarcts, as emphasized in the extensive review by Scholz and Nieto.[13] Nevertheless, a number of observers have laid great stress on the relationship between cerebral hyalinosis and hypertensive cerebral hemorrhage, notably Westphal and Bär,[3] Rühl,[12] Staemmler,[17] Anders and Eicke,[18] Eicke,[19] Matuoka,[14,15] and Smith,[16] although we must allow for differences in terminology and emphasis. Those forms of hyalinosis related to hypertension differ from those observed in normotensive persons in showing the inflammatory changes and the evidence of blood extravasation already described. The difference may be more readily appreciated if one distinguishes between the fibrinoid and the collagenous forms of cerebral hyalinosis, since it is the former which is almost exclusively related to hypertension, whereas the latter is related in some instances and not in others. The distinction may be difficult, but is often possible with hematoxylin and eosin stains. The distinction can be made with ease with the azocarmine and phosphotungstic acid hematoxylin techniques, as outlined above.

It is of considerable interest that in our material this hypertensive fibrinoid arteritis is limited to the brain. Clinically, it is recognized that gross hemorrhage associated with hypertension occurs almost exclusively in the brain, from the nasal mucosa, and in the retina. It is known that the cerebral arteries differ anatomically from those in other organs, being thinner, and containing less elastic tissue, and this concentrated in the internal lamella. They reveal differences pathologically as well, being affected by saccular aneurysms of a type only rarely paralleled in other organs.[30] The cellular

responses of the capillary endothelial cells in the brain are far severer than in other organs.[31] It is therefore not surprising that the cerebral arteries should commonly react in hypertension in a fashion only rarely observed elsewhere.

Nevertheless, the association of hypertension and necrotizing and fibrinoid changes in arteries of other organs has been described. Zeek and her collaborators, Smith, Zeek and associates,[32-36] segregated an entity, which they would call periarteritis nodosa, from the entire group of fibrinoid arterial necroses generally known by this name, and implied that this restricted entity is related to hypertension. The vasular lesions they described resemble those being set forth in the brain in presenting a fibrinoid change with a pleomorphic inflammatory infiltrate, in being associated with the formation of small aneurysms, and in showing a tendency to chronicity and healing. The cerebral lesions differ from those of Zeek's periarteritis nodosa in involving veins in rare instances, in not starting regularly in the intima, and in containing occasional giant cells in the inflammatory infiltrate. In these latter features, the cerebral lesions more closely resemble Zeek's hypersensitivity angiitis, a fibrinoid arteritis related to allergy and often designated as periarteritis nodosa by others. The brain is not a site of predilection for lesions in classical periarteritis nodosa. Arterial lesions like those of periarteritis nodosa have been reported in the organs of patients with "malignant" hypertension[35] and in the lungs in cases of pulmonary hypertension.[37] On the other hand, similar arterial lesions in surgically removed appendices have been reported in the absence of evidence of a serious disseminated disease or of hypertension.[38,39]

A fibrinoid arteritis, most frequently splanchnic,[32,40-42] occasionally cerebral as well,[43-46] has been observed in experimental animals rendered hypertensive by a variety of means. Among the factors involved in these experiments which may be relevant to the human situation are the activity of adrenal hormones, as in stress, and the influence of salt intake. One may speculate on the possibility that a low-salt diet, perhaps not as low as that required to lower the blood pressure, might nonetheless prevent this cerebral arteritis and cerebral hemorrhage.

It is noted that the fibrinoid arteritis was found in the brains of 15 cases of hypertensive cerebral hemorrhage, but not in the other 16 cases encountered in the same period of time, though studied with equal diligence. This failure may be due to the inadequacy of the search, despite its diligence, or to the self-destruction of the only altered vessels by the resulting hemorrhage. The arteritis was also found fortuitously in the brains of seven of a very much larger number of hypertensive cases without cerebral hemorrhage, these having been studied in only routine fashion.

Summary

The occurrence of a fibrinoid arteritis affecting the cerebral vessels of hypertensive patients with and without concomitant hemorrhage is noted in the absence of similar changes in other organs. It is suggested that this arteritis may be related to the gross cerebral hemorrhage noted in some such patients.

These arterial changes have been described in the past, as has their relationship to cerebral hemorrhage. The concept has failed to achieve universal acceptance, possibly because the specific arteritis has been submerged in a large group of arterial changes of somewhat similar appearance, many of which are unrelated to hypertension and the whole generally characterized as hyalinosis. With phosphotungstic acid hematoxylin and the azocarmine stains, the fibrinoid arteritis may be readily segregated from other forms of hyalinosis by the presence in the vessel wall of materials staining blue with the former stain and red with the latter. When so segregated, the relationship of this arteritic change, hyper-

tension, and cerebral hemorrhage becomes apparent.

A similar arteritis, most frequently splanchnic, is observed in animals rendered hypertensive by various means. The occurrence of an arteritis in animals with experimentally induced hypertension provides a parallel for the process postulated for the human brain and suggests the possibility that some of the factors related to the experimental situation may be applicable to the human. In this sense, a low-salt diet which prevents or decreases the intensity of the experimental arteritis may possibly prevent the cerebral arteritis of hypertensive patients, and prevent the occurrence of cerebral hemorrhage even if the blood pressure is not lowered.

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Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Robert S. Schwab, M.D., President, Presiding

Regular Meeting, Nov. 20, 1958

Diabetes Mellitus and Syndromes of the Central and Peripheral Nervous System. Dr. John F. Sullivan and Dr. Robert E. Flynn.

Included in this review of patients with diabetes mellitus are 58 with cranial and peripheral neuropathy, 37 with cerebrovascular disease, and 21 with spinal cord syndromes, which may be related to the diabetes. Diabetic neuropathy, in the majority of cases, can be divided into two clinically distinct syndromes: a distal, essentially symmetrical sensory neuropathy, and an asymmetrical, predominantly motor mononeuropathy or radiculopathy. Involvement of the third, sixth, and seventh cranial nerves occurs fairly commonly and clinically has features similar to the mononeuropathy. Either might occur as the first evidence of mild diabetes; the onset is usually acute and the prognosis good, the latter being independent of diabetic control.

Cerebrovascular disease in diabetes is characterized by the frequency of minor or transient "strokes," dementia, and the development of symptomatic epilepsy.

Diabetes and spinal cord syndromes of an atypical type coincide with a frequency that suggests a relationship. Of 21 diabetic patients, a diagnosis of cervical spondylosis was made in 7, of amyotrophic lateral sclerosis in 7, of syringomyelia in 2, and of dystrophia myotonica in 1. In two cases the disease was designated as myelopathy of unknown cause, in one as diabetic amyotrophy, and in one as diabetic myelopathy. As a partial answer, we suggest that the spinal cord in diabetics cannot tolerate displacement or distortion, such as may occur with cervical spondylosis. The possible role of a specific diabetic vascular disease was discussed in relation to the asymmetrical peripheral and cranial neuropathy, the liability to small strokes, the development of seizures, and the damage to spinal cord in cervical spondylosis.

Discussion

Dr. Robert S. Schwab: Is this syndrome a vitamin B disturbance, or is it related to vascular disease from the diabetes?

Dr. Samuel H. Epstein: Postmortem material in cases of diabetes with neurologic disorders, such as tabes or PMA, suggests that this is diabetes and a neurologic disease in the same patient, a simple coincidence.

Dr. Charles A. Kane: I have seen three patients with diabetic neuropathy with amyotrophy. This syndrome occurs in an unusual number of diabetics without peripheral vascular disease. Is this so in Dr. Sullivan's series?

Dr. Samuel Bogoch, Waverly, Mass.: Dr. Sullivan said some of his patients did not have glycosuria. Are there abnormal glucose tolerance curves in other neurologic diseases?

Dr. Paul B. Jossmann: I cite 12 cases of bilateral "sciatica," all with diabetes, the latter having not been diagnosed previously. Diabetes should be considered in the differential diagnosis of bilateral sciatica.

Dr. Philip R. Doige: We have not seen in diabetic children the complications described this evening.

Dr. Norman Geschwind: Amyotrophic lateral sclerosis, with abnormal glucose tolerance tests, was reported in October, 1958.

Dr. John F. Sullivan: Dr. Schwab asked a difficult question. I feel from the eyeground examination of many diabetic patients that there must be a specific disease of small blood vessels. Dr. Kane's remark that one should be very careful in terminology is one with which I agree. These patients with atypical syndromes are also diabetic. If there is an etiologic relationship, we have not demonstrated it. Dr. Jossmann's experience and ours are similar, since the sciatic and femoral nerves are the two most commonly involved. Dr. Geschwind's report of Dr. Matthews' article in the October, 1958, *Proceedings of the Royal Society of Medicine*, in which abnormal glucose tolerance tests are reported in amyotrophic lateral sclerosis, came as a surprise. Perhaps the basic metabolic error in amyotrophic lateral sclerosis is also associated with an abnormal glucose metabolism. In answer to Dr. Bogoch: I am not familiar with abnormalities of the glucose tolerance curve in other chronic neurologic disease.

Cerebral Manifestations of Cyanocobalamin (Vitamin B_{12}) Deficiency, Including the Report of a Case. DR. JUSTIN M. HOPE and DR. JAMES S. WIENER.

The cerebral manifestations of vitamin B_{12} deficiency have long been one of the less well-known facets of pernicious anemia. The reversibility of the mental aberrations depends mainly on the duration of the illness before the institution of effective therapy. Therefore early diagnosis is extremely important. Since none of the mental symptoms are consistently characteristic, the diagnosis depends first upon the physician's awareness of the existence of the disorder and, in the absence of anemia, the determination of the cyanocobalamin level in the serum and the use of the Schilling test. The essential cerebral pathology consists of degeneration of white matter, with little or no proliferation of fibrous glia. The pathologic degenerative process appears to be related to the decrease in cerebral metabolism as a result of the deficiency state rather than as a result of the anemia.

The case report is that of a 42-year-old housewife who was admitted to the New England Center Hospital because of a severe depression. Examination of the mental status revealed depression of mood, marked retardation, and overt paranoid ideation. Laboratory findings were macrocytosis, achlorhydria, and a serum cyanocobalamin level of 28μg. (normal, 150μg.-1,000μg.). Treatment with large doses of the vitamin intramuscularly was begun, and within a month she showed significant improvement.

Discussion

DR. ROBERT S. SCHWAB: Does this syndrome exist in the presence of free hydrochloric acid? Does the indiscriminate use of cyanocobalamin in small amounts hide this condition for quite a long time?

DR. SAMUEL H. EPSTEIN: This paper emphasizes the value of adequate physical and neurologic examination of patients with mental illness. Psychiatrists have been aware of mental illnesses associated with combined system disease. Such cases are the ones that used to be mistakenly diagnosed as involutional melancholia (paranoid type).

DR. MADELAINE R. BROWN: I should like to ask whether any systematic tests for vitamin B_{12} are being used in our state hospitals.

DR. JUSTIN M. HOPE: In answer to Dr. Brown's comment: I think not. I can speak for Worcester State Hospital, where they are not doing systematic tests for vitamin B_{12}.

In answer to Dr. Schwab: I should think the diagnosis of mental symptoms due to pernicious anemia would be extremely unlikely, in the absence of free hydrochloride acid.

The other comment relative to vitamin B_{12} modifying the picture is true. It altered the blood in our patient, and the bone marrow. Patients with pernicious anemia who have mental symptoms don't get better on small doses of cyanocobalamin, although the blood picture does change. The reverse occurs. This woman received cyanocobalamin in small doses, yet developed mental symptoms.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, Dec. 18, 1958

Observations on the Treatment of Obsessive-Compulsive Neuroses with the Energizers. DR. ROBERT ARNOT.

Each really different psychopharmaceutic agent that is developed provides us with an opportunity to make new observations on the classical psychiatric illnesses. The energizers have been observed to have a definite ameliorating effect on the obsessive-compulsive neuroses.

Janet had considered that these illnesses were a psychasthenia. Von Gebsattel described one patient as having an "incapacity to let his energies stream into the implementation of a task-oriented self-development." We can now observe that these psychological states have a physiological substratum that is altered by treatment with the energizers.

With medication at least five different, but related, changes have been observed in these obsessed, depressed, compulsive, fearful, guilt-ridden, scrupulous patients. 1. The output of physical energy was increased to accomplish the tasks which the patient had set for herself to do. Feelings of guilt and inadequacy were thereby reduced. 2. An elevation of mood was observed that enabled the patient to regard her symptoms and problems in a more hopeful, less fearful manner. 3. An increased ability to reason and to develop ideas was observed. This enabled the patient to reason her way more constructively through her problems and illness. One woman stated that before medication she felt "scattered," whereas with it she felt "collected." "If you are feeling well, you are collected. If you are collected, you are going to make a sound appraisal of things." The state of mind, she said, was quite different from the "dull," "trapped" condition she had experienced with chlorpromazine.

4. The compulsions were observed to be less forceful. "And I don't do the crazy things I used to do." "I said to my niece, my hands are dirty; I don't care." 5. A forthrightness was observed in relation to the provocative person, who often lives in close proximity to the patient with the obsessive-compulsive neurosis. "I had an argument with my father (whom she "hates"), and it didn't bother me."

Discussion

Dr. Robert S. Schwab suggested that the term "so-called psychic energizers" would be better than the simple word itself. Dr. William N. Hughes stated that he has used iproniazid (Marsalid) sparingly because of the dangers of jaundice, which was fatal in over one-half the cases. Dr. E. P. Richardson Jr. wondered if it was necessary to continue permanently the use of this medicine. In closing, Dr. Arnot defended the use of the simple term "energizers." He emphasized that two of his patients, physicians, were definitely more active, and perhaps a little hypomanic, and reported definitely that something specific had really happened. He commented on the fact that 100 mg. a day was safe enough, but probably would not be effective. He concluded by stating that the best technique was to use full doses at the start and then reduce them as soon as possible.

Spinal Epidural Hematoma: A Complication of Anticoagulant Therapy. Dr. Simon Horenstein, Dr. D. Bertram Winer (by invitation), and Dr. Albert Starr (by invitation).

The syndrome of nontraumatic spinal epidural hematoma is characterized by the acute development of back pain, the relatively slow development of spinal-cord and nerve-root deficit, and subsequent spinal block if the hematoma is of sufficient mass. The cerebrospinal fluid contains a peculiar brownish pigment, which may be methemoglobin. The subject of this report had been maintained on bishydroxycoumarin U. S. P. (Dicoumarol) for 11 months at an average prothrombin time of 12%, when, after defecation, she developed acute midthoracic pain, which progressed over six hours to paralysis of both lower limbs, loss of all sensation below the eighth thoracic segment, and loss of voluntary bowel and bladder function. The lower level of a dynamic block was found by myelography to be at T-10. An epidural clot, about 7 cm. in length and 0.5 cm. in thickness, was found on the dorsum of the dura between the 7th and the 10th thoracic spine. The source of bleeding was not identified. There has been no significant recovery.

Discussion

Dr. Joseph M. Foley felt that at the present time anticoagulants were being used without adequate reason in many cases. He had not seen a case similar to the reported one, but felt that some of the pathological material showed that bleeding was due to the disease, and not to the therapy. Dr. Richardson confirmed Dr. Foley's statement and said that he can be sure of only one case in which therapy was implicated as the cause of the bleeding. Dr. Charles Kane emphasized the risks of anticoagulant therapy in relation to the possible advantages. Dr. Harold W. Williams cited four cases of his own in which he felt that the therapy might have contributed to the bleeding.

In closing, Dr. Horenstein stated that he had recently heard of five patients dying with subdural hematomas who had been receiving anticoagulation therapy.

Geographic Distribution of Multiple Sclerosis and Cosmic-Ray Intensities. Dr. John S. Barlow.

The geographic distribution of multiple sclerosis (for which reports indicate relatively frequent occurrence in the northern parts of the United States and Europe, but relatively infrequent occurrence in Africa, South America, and the Orient) has not appeared to be well correlated with any of the possible factors invoked heretofore (e. g., climate, or dietary fat intake) when all of the available data are examined. It seemed of interest, therefore, to compare the distribution of this disease with that for cosmic-ray intensities, which also exhibits a geographic distribution. The variation in intensity of these very high-energy particles arriving from outer space is determined by the effect on them of the earth's magnetic field, and hence is correlated with geomagnetic latitude, determinable from the corresponding geographic latitude and longitude by means of conversion charts. For the present purpose, several sets of morbidity and mortality data were plotted against geomagnetic latitude, and good agreement was observed among them, despite a number of uncertainties about the accuracy of each set of data considered individually. From one of these (Kurland, 1957), and from a recently published chart of isointensity lines of cosmic-ray particles incident upon the top of the atmosphere (Webber, 1958), a map was constructed indicating the expected world-wide distribution of the disease. Predictions made from this map are in excellent agreement with currently available data for a number of widely separated areas. These preliminary results suggest consideration of new approaches in the study of this disease.

Discussion

Dr. Charles Kane asked whether these remarkable findings might not be due to an increased density of the atmosphere at the equator, which would "filter out" more cosmic rays than in non-

tropical areas. Dr. Foley asked whether the same comparison would be practical with rheumatic fever. Dr. Horenstein asked whether there had been any pathological observations on animals returned from the stratosphere or ionosphere.

In closing, Dr. Barlow made the following points: The decrease in cosmic-ray intensities with decreasing latitude results primarily from the filtering effect of the earth's magnetic field, although at all latitudes the atmosphere generally exerts a very considerable additional filtering effect. Some data have already been collected for examination of the distribution of rheumatic fever. Comparison of the lesions of multiple sclerosis with those of neuropathological studies on animals exposed to cosmic rays at high altitude has not yet been made.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

Clarence C. Hare, M.D., Chairman, Section of Neurology and Psychiatry, Presiding

Combined Meeting, Nov. 11, 1958

Clinical Implications of Spinal Fluid Lactic Dehydrogenase Activity. Dr. Felix Wróblewski.

In normal persons and in patients without central nervous system disease, spinal fluid lactic dehydrogenase is less than 40 units per milliliter. The spinal fluid level varies independently of the plasma or serum activity. In most persons without central nervous system disease, and in those with degenerative and nonspecific states of the central nervous system, the spinal fluid activity is below 40 units per milliliter. In patients with intracerebral or meningeal leukemia, lymphoma, or metastatic carcinoma, the spinal fluid lactic dehydrogenase is consistently above the normal range. Acute meningitis is associated with marked increases in spinal fluid lactic dehydrogenase activity, which returns toward the normal range with clinical response of meningitis to treatment. Various mechanisms appear to be involved in the elevation of spinal fluid lactic dehydrogenase.

Discussion

Dr. Gerald Harvey Klingon: This test has proved to be a valuable adjunct in the diagnosis of metastatic central nervous system tumors. As population ages, a still greater incidence of such tumors is expected. Radiation therapy is usually the treatment of choice, and a test which aids in diagnosis without necessarily resorting to burdensome procedures has obvious merit. Serial determinations add to its value because a rising level indicates tumor, and a falling one, another cause. Employment of this test and its correlation with final diagnostic data, by neurologic and neurosurgical services, should serve to determine its ultimate place in neurologic diagnosis.

Dr. Israel S. Wechsler: May I tell in a few brief words the effect of enzymes on sugar metabolism? I refer to the case of a young man who showed moral lapses, memory disturbances, and dysarthria. He evidently had Addison's disease and marked hypoglycemia. At first he responded to oral and intravenous administration of sugar and then failed to respond. We discovered a high pyruvate content in the spinal fluid and evidence of interference of pyruvate breakdown for absorption by the brain. Administration of thiamine, acting as coenzyme, reduced the pyruvate in the fluid and permitted absorption by the brain to the extent that the symptoms largely improved and the electroencephalogram returned to normal.

Dr. Otto M. Bergen: I would appreciate a statement by Dr. Wróblewski regarding the discordance between his first published findings on lactic dehydrogenase activity and those presented today.

I am impressed with the absence of increased lactic dehydrogenase activity in cerebral infarction. This is in contrast to the elevated glutamic oxalacetic transamiñase (GOT) levels of the spinal fluids of a large number of patients with cerebral infarction, as reported by various investigators and confirmed by our studies at Metropolitan Medical Center. This might, indeed, be an aid in the differential diagnosis of problem cases.

Dr. Felix Wróblewski: Lactic dehydrogenase activity in normal spinal fluid, in the absence of central nervous system disease, does not vary more than 20% and that degree of fluctuation is taken into account in attempting to calculate the upper limit of normal as 40 units per milliliter. In pathologic conditions, with brain tumors, the fluctuation may be appreciable. Actually the fluctuation may be as high as 50% to 100%. Usually these fluctuations stay above the normal range. However, our experience indicates that the fluctuations do not conflict with the conclusions we can derive from the information.

Early Treatment of Ruptured Intracranial Aneurysms of the Circle of Willis with Special Clip Technique. Dr. J. Lawrence Pool.

Because an intracranial aneurysm can explode within the head at any moment, prompt surgical treatment is important, preferably by direct intracranial obliteration of the aneurysm, as carotid ligation in the neck does not always prevent recurrent hemorrhage, especially for anterior and middle cerebral artery aneurysms. Early surgical treatment is also urged when the age and condition of the patient permit, to prevent permanent neurologic deficits due to progressive cerebral vasospasm, as well as to prevent the high mortality following nonsurgical or conservative therapy. Bilateral angiography is essential to determine the adequacy of circulation through the circle of Willis and the presence of multiple aneurysms. The latter does not necessarily contraindicate surgery. Technical developments that now make early intracranial surgery of ruptured berry aneurysms safer and easier include hypothermia and small removable clips to reduce temporarily blood flow in an aneurysm until it can be permanently clipped.

Patients who are over 50 to 55 years of age and/or comatose are generally not suitable candidates for intracranial surgery. Of the 23 patients reported, 14 less than 50 years of age and in reasonably good condition were operated upon within two weeks of subarachnoid hemorrhage. There was a mortality rate of only 14%, which compares most favorably with the higher death rate for this period when no surgery was done. Fully one-half were operated upon within six days and one-third within three days.

Discussion

Dr. Melvin D. Yahr: Dr. Pool has given a very lucid and comprehensive discussion of the clinical manifestations, complications, and serious implications of intracranial aneurysms. His results of surgical therapy are impressive and especially significant, since operation was carried out within the so-called critical period, that is, the first two weeks following hemorrhage. Unfortunately, it is difficult to evaluate the benefits of surgery for aneurysms, as there are few, if any, significant studies on nonsurgical cases.

I should like to ask two questions: 1. What is the mortality rate in the surgical group, and what is the type of postoperative neurologic deficit? 2. In patients who died as a result of operation, were the pathologic findings related to the original lesion or to a technical factor of the operation?

Dr. Israel S. Wechsler: I agree in the main with the views expressed by Dr. Pool. Clearly, arteriography is the only positive method of revealing an aneurysm, but the fact is that in a large percentage of cases the bleeding is due not to aneurysms but to other cerebral vascular anomalies. Rupture of a vascular anomaly is not as threatening to life as a ruptured aneurysm. In the former cases repeated hemorrhages can occur; at Mount Sinai Hospital we had patients who had repeated subarachnoid bleeding; one had 16 episodes.

Dr. Lawrence H. Gahagan: I should like to inquire about the increasing safety of angiography. I understand that the procedure is less hazardous than it was a few years ago. What is the present incidence of serious complications?

Dr. J. Lawrence Pool: I would emphasize again that 82% of these patients were operated upon in the first 12 hours to 12 days after subarachnoid hemorrhage, some during the actual development of neurologic signs. I think, therefore, that some lives were definitely saved by this early surgery.

As to morbidity (hemiparesis, confusion, etc.), my patients under 50 had a morbidity of approximately 10%, and those over 50 a morbidity of 33%.

As to the autopsy findings, recurrent hemorrhage after merely wrapping one aneurysm with muscle, and progressive cerebral edema with uncal herniation were two causes of death. Multiple microscopic infarcts may be found with more study.

Early Recognition of Neurologic Conditions in a Psychiatric Hospital. Dr. Curtis T. Prout and Dr. Kenneth Hall Epple, White Plains, N. Y.

Various neurologic or organic conditions may appear in the guise of psychiatric syndromes of the functional type. Perhaps some agent or process has impaired the functioning of the brain tissue, presenting a deficit in intellectual capacity. On the other hand, the personality functioning may be sufficiently distorted that the presenting symptomatology may initially be characteristic of a functional illness. With this in mind, 3,500 consecutive cases admitted at the New York Hospital-Westchester Division were reviewed. About 5% had presented some existing basic or associated neurologic condition, which appeared with equal frequency in men and women. When correlated with the psychiatric diagnoses, there appeared to be no consistent relationship.

Among the 5% with neurologic findings, there was a wide diversification of entities. New growths and space-occupying lesions were among the most dramatic findings.

Two case reports were presented. In the first a meningioma had been completely disguised by psychiatric symptoms. In the second a subdural hematoma was alertly discovered and drained, followed by subsequent treatment of the psychiatric condition.

The paper serves as a renewed warning that a high index of suspicion should be maintained regarding organic conditions masked by psychiatric symptoms and vice versa.

Discussion

DR. ROBERT B. MCGRAW: This paper is simple in some senses, but it is extremely valuable, particularly to psychiatrists, I think, that this point of view be presented. It used to be that the neurologists overexamined patients. Then came the era of psychiatric complacency, and diagnoses were missed. The importance of compensating for a neurologic deficit, or denial of neurologic deficit, is suggested in the presentation, and I like very much the phrase used by the authors, "maintaining a high index of suspicion," which is the antithesis of psychiatric complacency. This alertness to the existence of some possible neurologic condition is probably even more important than any routine examination.

I would like to mention the use of psychological tests, including the Rorschach, which sometimes can aid in the evaluation of the organic component, or sometimes turn up the existence of an organic condition.

DR. CURTIS T. PROUT: The point of using the Rorschach test or psychological search for organicity is an important one; and when the patient can cooperate and is able to think, this is a very valuable adjunct. The mechanisms or the procedures often used by the psychologists now are quite effective in showing, as they term it, organicity, which lends support to the diagnosis. There are also neurologic symptoms which suggest psychiatric conditions, the reverse of what we spoke of, and there, too, we have to be on the alert for the psychiatric condition with the presenting neurologic condition.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

Joint Meeting, Jan. 13, 1959

The Present-Day Meaning of Insight. DR. JANE F. O'NEIL.

Recent Experiences with Chromophobe Adenomata. DR. HOWARD PAUL KRIEGER.

Of 127 chromophobe adenomata seen at the Mount Sinai Hospital, New York, in the past 10 years, only one-third were verified histologically because of the decreasing rate of surgical intervention. Eighty-seven per cent of cases had visual field defects, which could usually be found by confrontation tests if colored targets were used with the technique of double simultaneous stimulation. Eighty per cent had EEG's, of which 60% showed symmetrical diffuse 4-7 per second activity unrelated to adrenal cortex insufficiency. About 0.5% had convulsions, apparently related to cerebral destruction and endocrine defect combined. Seventy per cent had endocrinopathies, which were rarely a source of chief complaint. Hormonal replacement therapy was efficacious.

About 70% of patients were successfully treated with radiotherapy alone (4,000 r). Eight per cent required multiple courses. In cases in which surgical intervention and radiotherapy were of little use, subsequent surgical intervention was also of little help. The results with surgical intervention alone were no better than those with radiotherapy and involved operative risk in addition. The success with radiotherapy alone, as compared with surgical therapy or combined surgery and radiotherapy, suggests that radiotherapy is the treatment of choice except in those few cases of rapid, unremitting loss of vision unaided by radiotherapy when it can be ascertained that the radiotherapy itself is not the cause of a temporary increase in visual deficit. If it is the cause of such deficit or a parasellar syndrome, spontaneous recovery may be expected.

Discussion

DR. LOUIS J. SOFFER: The most important indication for surgical intervention in instances of chromophobe adenoma of the adenohypophysis is rapid loss of vision. It is a wise precaution to bear in mind that patients with chromophobe adenoma of the pituitary may have adrenal cortex insufficiency. Before such patients are subjected to any surgical procedure, the adrenocortical status should be carefully investigated, or such patients should be treated prophylactically with adrenal cortex replacement therapy.

DR. PHILIP LEVIN: Dr. Krieger mentioned a case in which there were two surgical procedures on a chromophobe adenoma, and after the second the dose of thyroid and steroids was decreased, or could be decreased. I do not understand the mechanism.

DR. JOSEPH RANSOHOFF: The aim of x-ray therapy or/and surgery in the therapy of pituitary adenoma is solely that of preservation of vision—it is our practice at the Neurological Institute of New York to establish a level of visual acuity below which we will not give radiotherapy but resort at once to surgery.

DR. FRITZ CRAMER: The unusual number of carcinomas cited, and of atypical signs and symp-

toms, raises the question whether conditions other than pituitary adenomas were presented.

A case in point will illustrate the possible significance of unusual symptoms, as well as emphasize the accepted indications for surgery, as just cited. A woman had long-standing, unexplained right optic atrophy. She developed a new and typical syndrome of pituitary adenoma with rapid chiasmic compression. X-ray therapy was ineffectual. At operation I found two separate lesions.

In addition to the adenoma compressing the chiasm from below, the right optic nerve was distorted and compressed by a medially displaced, adherent internal carotid artery. Vision was restored to near normal in the right eye despite the duration of the compression.

DR. HOWARD PAUL KRIEGER: Dr. Levin, perhaps decrease in tumor size allows the remaining pituitary tissue to function more normally.

I agree with Dr. Cramer that some of the complications described here are unusual. As stated, I purposefully omitted the garden variety of chief complaints and symptoms. The unusual complications described occurred, however, in histologically proved cases of chromophobe adenoma, as well as in suspected cases in which all possible procedures short of biopsy were done to establish the diagnosis. Convulsions occurred in two histologically proved chromophobe tumors. In a third case, they were apparently the result of temporal-lobe disease secondary to a large mass, which first was intrasellar. In another case convulsions followed unsuccessful surgical intervention for rhinorrhea.

After-Contraction Phenomenon as a Measure of Sympatholytic Action. DR. MILTON R. SAPIRSTEIN, DR. ROBERT JAFFE, and DR. STANLEY BERNSTEIN.

The after-contraction phenomenon was studied from the vantage point of its fluctuation under the influence of varying states of emotional disturbance. Control studies were done with 200 cases in which intensive clinical observation and psychologic tests were available. Simultaneous electromyographic observations were made; the influence of various drugs was studied, and the fluctuations were correlated with the Funkenstein test.

The following conclusions were drawn from a two-year study: The after-contraction diminishes with a downhill clinical course; it increases with clinical improvement. The after-contraction invariably disappears with the depressed state, reemerges with acting out or the capacity to express emotions, especially aggressive feelings. There was a direct correlation between the sympatholytic response on the Funkenstein test and the disappearance of the after-contraction. When shock therapy was effective in lifting the depression (and reversing the Funkenstein response), the after-contraction returned. The after-contraction is a measure in the intact human being of the sympathetic-parasympathetic balance. Psychoanalytic correlations were made which indicated that when the defense against anxiety took an inhibitory or a depressive form, the after-contraction diminished. On the other hand, when anxiety led to a rage response, the after-contraction was strong. Sympatholytic drugs—chlorpromazine (Thorazine), reserpine (Serpasil)—diminished the after-contraction.

Discussion

DR. LOUIS LINN: Recent years have seen a growing interest in the evaluation of psychiatric patients by means of objective laboratory methods. It is in this current of research that I should place the work by Sapirstein and his co-workers. On the basis of our experience on the psychiatric ward at the Mount Sinai Hospital, I would want a patient whom I was starting on ECT to have a *negative* after-contraction. Conversely, the presence of a good positive after-contraction would argue against the use of ECT. A particular advantage of this procedure is its simplicity not only from the experimenter's point of view but also in terms of its nontraumatic impact on most patients.

DR. CLARENCE C. HARE: Will you tell us what happened to the other 30% of the normals?

DR. MILTON R. SAPIRSTEIN: Most of the 30% of the normal population who do not have an after-contraction develop a normal after-contraction after repeated testing—when they learn to relax with the procedure and lose their fear of looking silly or being embarrassed. There will always be a group of "so-called" normals who are afraid of "losing control," who are incapable of any normal self-assertiveness, or those who are masking an underlying depressive reaction to anxiety. These continue to have an absent after-contraction.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Harold R. Merwarth, M.D., President, New York Neurological Society, Presiding

Combined Meeting, Oct. 9, 1958

Presidential Address: Reevaluation of Hemiplegia of Venous Origin. DR. HAROLD R. MERWARTH, Brooklyn.

The paralysis, in its initial phase, is one of an insufficiency of drainage rather than a complete occlusion, and the characteristic findings are of cortical origin. The clinical features of a cortical venous type of hemiplegia are as follows: 1. Motor paralysis, involving the lower extremity most severly, the foot most of all, then the shoulder, and a sparing of the hand and finger movements. 2. Early rigidity of the muscle in the paralyzed limb. This rigidity is destructive. It may be so firm that the limb cannot be moved forcibly at the various joints. 3. A peculiar type of plasticity, when passive movement is possible. 4. Sensory changes of a cortical type, postural appreciation and touch localization being disturbed, and pinprick being relatively intact. 5. A conspicuous lack of speech disorder. 6. An impressive mental alertness. The patient does not appear ill. 7. Variation in the degree of weakness or paralysis—from absence of movement to fairly good function in a short space of time, or while the patient is being examined. Equally striking is the fluctuation in muscle tone from a plastic molding type to a steel-like rigidity. These physical findings, when correlated, add up to a syndrome which is clinically diagnosable, viz., the Syndrome of the Rolandic vein, a hemiplegia of cortical venous origin.

The Extraspinal Origin of Spinal Cord Vascular Disease. DR. ALBERT W. COOK, Brooklyn.

The clinical entity consisting of dysfunction of the lower spinal cord and occlusion of the abdominal aorta without the usual signs in the lower extremities of such a lesion was described. The dysfunction of the spinal cord is represented by the usual findings of a transverse lesion at the seventh to the ninth thoracic segment; however, there is often hyporeflexia or areflexia in the lower extremities, even though the sign of Babinski is present bilaterally. In almost all cases the usual procedures designed to detect disease within the spinal canal, including exploratory laminectomy, were carried out, without establishing the basis for the syndrome. Abdominal aortography showed occlusion of the distal abdominal aorta, even though signs in the lower extremities of such a vascular lesion were lacking. A review of the literature did not disclose any similar case in which aortography had been done ante mortem. The relationship of this entity to that of so-called anterior spinal artery syndrome was discussed. It was suggested that in many such instances extraspinal vascular disease of the spinal cord may, in truth, be the basic issue, rather than intraspinal vascular occlusions, which are only rarely substantiated anatomically.

Discussion

DR. H. HOUSTON MERRITT: Dr. Cook has pointed out that arteriosclerosis of the spinal arteries is extremely rare and that the diagnosis of thrombosis of the anterior spinal artery is usually erroneous. Dr. Cook also pointed out one cause of damage to the spinal cord by vascular disease, that is, thrombosis of the abdominal aorta. I believe he is the first to have made this diagnosis on clinical grounds prior to the performance of angiography.

There are several other diseases of extraspinal vessels that can cause the syndrome described by Dr. Cook. One of these is a dissecting aneurysm of the aorta, and is the result of extension of the lesion into one of the main contributing vessels of the spinal cord. Another, and perhaps the commonest, cause of occlusion of the spinal vessels is tumors outside the bony spine, particularly metastatic carcinomas and tumors of the lymphogenous group which form a cuff around the vessels and produce thrombosis.

This paper is a valuable contribution to the problem of acute transverse myelitis. I hope it will result in a decrease in the number of reports on thrombosis of the anterior spinal artery without pathologic verification.

DR. MORTIMER F. SHAPIRO: Was the constitution of the spinal fluid normal?

DR. GEORGE H. HYSLOP: I am glad Dr. Merritt called our attention to cuffs around the vessels of the spinal cord. It is a much commoner situation than aortic obstruction. In my experience at Memorial Hospital I have seen plenty of such material, and I learned long ago that if we found no bony damage in x-rays, and if there was no subarachnoid block, we should waste no time but proceed with irradiation. In a certain percentage of cases, it temporarily improved the cord condition and gave palliation for three to six months.

DR. I. M. TARLOV: Probably many of us will be seeing cases similar to Dr. Cook's, in which spinal cord ischemia is induced during heart operations. I recently saw a 2-year-old child whose flaccid paralysis followed a 40-minute occlusion of

the descending aorta during a cardiac operation. The pathologic substrate was doubtless an almost total gray matter necrosis, such as occurs in dogs after a 50-minute aortic occlusion. An approximately 45-minute occlusion produces extreme hind-limb hypertonus, due to a spinal interneuronal lesion. We shall probably see this syndrome of lower-limb rigidity in man, too, in view of the frequency of operations necessitating temporary aortic occlusion.

DR. MORRIS B. BENDER: I should like to ask Dr. Cook whether he has considered the numerous cases one sees at autopsy in which the aorta is probably occluded by an abdominal aneurysm, and yet there are no symptoms referable to the spinal cord. I wonder whether Dr. Cook took these cases into consideration as a background for his cases.

DR. ALBERT W. COOK, Brooklyn: I should like, first, to thank the discussers for their comments. After our initial experiences, the classic history and physical features of this syndrome have enabled us to predict the demonstration of aortic occlusion before aortography. The quantity of protein in the spinal fluid has never assumed significantly abnormal proportions. Time does not permit discussion of vascular lesions of the spinal cord of animals; however, it is sufficient to state that we have noted massive infarction in the spinal cord of dogs under the experimental conditions of the heart-lung pump-oxygenator. In all these circumstances, as well as in the situations mentioned by Dr. Bender, the essential feature was the adequacy of blood flow through the radicular arteries and/or even one major radicular trunk. When aortic occlusion occurs at levels demonstrated in the present group of patients, the presence of spinal cord infarction of the character shown indicates primary failure of circulation in the radicular arterial system. If this is adequate, spinal cord function may be maintained, even though there is occlusion of the abdominal aorta.

Syndrome of Isolated Amnesia. DR. MORRIS B. BENDER.

A series of 26 patients were observed to have a single episode of confusion, which lasted several hours. All of them were past the age of 50. The onset of the attack was sudden. The patient has a severe loss of immediate memory, incessantly repeating questions and not infrequently showing anxiety about his mental state and his inability to remember. He may be completely disoriented. Often he may get lost if he happens to be traveling. The marked mental confusion may last from one to six hours. Occasionally it has lasted as long as 48 hours before complete recovery ensued. Following this, there is a complete amnesia for all events that transpired during this period. It is of interest and significance that only one such episode occurred, and that there have been no recurrences, even in patients who have been observed for as long as eight years.

As for the anatomy and pathology of this condition, we have no information, since there have been no autopsies in this series. The etiology is just as obscure. Hysteria was excluded on clinical grounds. None of these patients whom we studied in detail showed evidence of a neoplasm, trauma, infection, or toxic-metabolic disease. There was no history of alcoholism. Although it is unlikely that the syndrome was caused by an occlusion of a single vessel, a general circulatory dysfunction of the brain may produce this type of clinical picture.

Discussion

DR. HANS STRAUSS: This paper is significant in that it points out that attacks of amnesia may occur only once in a particular patient. However, one cannot predict with certainty that they will not recur. In any case, one single attack of this disorder in the presence of negative neurologic findings should prevent us from making an unfavorable prognosis and from subjecting the patient to many diagnostic procedures. No electroencephalograms were obtained by me in any one of eight cases I have seen during the attack itself. After the attacks, only one patient showed a minor electroencephalographic abnormality, which, in this case, indicated a frontal lobe disturbance. Probably the basis of the amnestic states is a dysfunction of the hippocampal system, which may be paroxysmal in nature, but is more probably due to an insufficiency of local blood supply.

DR. SAMUEL BROCK: I have had the opportunity of observing a perfect instance of this syndrome brought about by the usual doses of meprobamate (Miltown). I am wondering how many of these patients may have had some kind of similar intoxication.

DR. MORRIS B. BENDER: First, I want to answer Dr. Brock. We considered the possibility of drug intoxication, but I cannot think of any of the patients who were taking drugs at the time of the attack. If they did, they did not tell their physician or me.

As for what Dr. Strauss said, we have a private debate about this; we differ often in our theories, but I do not think this is the place to start this debate. However, I do want to emphasize one point. The problem is to decide whether the patient with so-called amnesia is going to have one or more attacks of these symptoms. What I wanted to stress is that there are many cases which have only one attack over many years, and therefore this syndrome does not portend serious consequences.

Unusual Psychiatric Manifestations of Neurologic Disease. Capt. Felix H. Ocko (MC), U. S. N.

A summary is given of three cases which were seen on the neuropsychiatric service of the U. S. Naval Hospital at St. Albans, N. Y., and which prove the need for close clinical and neurologic examination, no matter how "disturbed" the patient may be.

All three cases were admitted in states of confusion with disordered behavior. The subsequent diagnoses were (1) acute subarachnoid hemorrhage, (2) abnormally low blood sodium level, and (3) meningococcic meningitis.

These examples are given to emphasize several points: (1) The line between organic and functional disease is frequently very fine, and there should be positive reasons for diagnosing either or both in the same patient; (2) any systemic disorder disturbing the metabolic processes, or any disease activity, will be manifested by a mental disturbance, and possibly manifestations of nervous system malfunction; (3) these phenomena do not obviate or exclude concurrent psychological processes which are the basis of personality organization and behavior, and which influence the total manifestations of the illness.

Discussion

Dr. S. Bernard Wortis: Dr. Ocko has focused our attention on psychiatric manifestations of neurologic (or general medical) disease. For the antique and dwindling minority of us trained in both psychiatry and neurology, this paper is most welcome, for it presents the opportunity to emphasize (1) a clinical attitude, (2) a training need, and (3) a dilemma that faces neuropsychiatric education.

The organic psychoses are too often neglected in the present-day concentration on dynamics, to the sad neglect of this wonderful clinical material that has much to teach us about brain and mental function. The acute and chronic brain syndrome emphasizes our need to get back to neurologic and psychiatric training. Too many of our present-day psychiatrists are too often isolated from neurophysiologic knowledge.

Dr. Israel S. Wechsler: Thank you, Dr. Ocko, for bringing the three cases to our attention. The real lesson to be derived from the presentation is that it is good psychiatric practice first to examine every patient medically and neurologically. It so happens that in the last few weeks I saw one patient who had been well all her life, became depressed, was investigated psychoanalytically, and was promptly administered electroshock. When I saw her, 10 days after the onset, the diagnosis was undoubtedly tumor of the brain. The second case was that of a middle-aged woman whose illness was diagnosed as a psychoneurosis and who underwent analysis for a few days. She had a typical virus meningitis. A third one, with onset of psychiatric symptoms, turned out to have had a subarachnoid hemorrhage. It is an old observation that a great many psychiatric manifestations have a neurologic background, and the prediction is now warranted that increasing knowledge of neuroanatomy, neurophysiology, biochemistry, and pharmacology will contribute to the scientific growth of psychiatry.

Capt. Felix H. Ocko (MC) U. S. N.: I should like to say but one thing, and to thank Dr. Wechsler for his comments. I happen to be analytically trained myself, and I feel that one field should not completely exclude the other. This is the point I want to make: I feel there are too many sharp divisions. I realize that no one can be expert in all these fields, but people have to be aware of them.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, Dec. 9, 1958

Cervical Myelopathy Due to Congenital Absence of the Odontoid Process. Gerhard H. Fromm (MC) and Emil Thelen (MC), U. S. N.

Since 1933, a total of 20 cases of congenital absence of the odontoid process have been reported. In four of these the anomaly was associated with spontaneous occurrence of cervical myelopathy; five patients suffered post-traumatic cervical-cord or root symptoms, and nine had orthopedic symptoms, either spontaneously or after neck injury.

The case of a 35-year-old Air Force sergeant who developed evidence of progressive cervical-cord damage is reported. The patient's symptoms started at the age of 31 with episodes of urinary retention. By the time he was hospitalized he also had nystagmus, spastic paresis of both lower extremities and the right upper extremity, sensory impairment in these limbs, and impotence. He was found to have congenital absence of the odontoid process with anterior and posterior dislocation of

C-1 on C-2 on head flexion and extension. A fusion of the occiput and C-1, C-2, and C-3 was carried out. Postoperatively, the patient improved in that his genitourinary difficulties disappeared, he regained the full use of his right upper extremity, and the motor deficit in his legs decreased.

Since the neurologic symptoms in our case and in those reported in the literature came on fairly late (at the age of 29 to 57), it appears that the spinal cord is injured gradually, probably with intermediate steps between the chronic dislocation and the resulting myelopathy. On the basis of the operative findings in one case and the autopsy results in two cases of delayed myelopathy after fracture of the odontoid process, the following mechanism is postulated: The repeated compression, angulation, and stretching to which the spinal cord is subjected results in meningeal irritation and hypertrophy. This, in turn, compromises the blood supply and eventually leads to degeneration of the affected segments of the spinal cord.

Discussion

DR. THOMAS I. HOEN: Absence of the odontoid process results in instability and false motion between the first and the second cervical vertebra. It is a chronic and progressive condition, which frequently leads to signs of compression of the spinal medulla. Fractures of the odontoid process and rupture of the transverse ligament of the atlas are two other conditions which produce the same clinical syndrome. The same treatment is indicated in all of these conditions, and it consists simply of fusion of the atlas to the axis. There is no indication whatever to fuse the vertebrae to the occiput, although it appears to be common practice to do so.

Clinicoanatomic Studies of the Syndrome of the Median Longitudinal Fasciculus. DR. MORTON NATHANSON, DR. NICHOLAS CHRISTOFF, and DR. PAUL J. ANDERSON.

Three cases of the median longitudinal fasciculus (MLF) syndrome with autopsy findings are described and compared with previously reported cases. The lesions in the present series are smaller and more discrete than in previous cases; however, they still are not confined to the MLF. The consistent feature in all such cases is that a lesion of the MLF produces paresis of adduction on attempted lateral gaze. Because of the frequency of its occurrence, dissociated or monocular nystagmus may also be attributed to destruction of the MLF. It cannot be stated with certainty whether other phenomena seen in this syndrome, such as vertical nystagmus, paresis of upward gaze, and ptosis, are due to destruction of the MLF or of surrounding structures. Portions of the paramedian reticular formation have been involved in all cases, and it is possible that some of the dysfunctions seen are a result of this.

In the two previously reported unilateral cases of the MLF syndrome and in the one case in the present group in which the symptoms were unilateral, the paresis of adduction was ipsilateral to the MLF involved. These findings are contradictory to the results of certain animal experiments which indicated that the MLF mediated adduction of the contralateral eye.

The nearly complete recovery of two of the cases in the present group, even though there were permanent lesions of the MLF, suggests that other pathways may be involved in the supranuclear mediation of such eye movements. This is further supported by the clinical observation of "incomplete" MLF syndromes after administration of barbiturate and the report of a case in which there was no anatomic change in the MLF, even though the syndrome was present during life.

Discussion

DR. MORRIS B. BENDER: It is most difficult to cull the information from the clinicopathologic material because of frequent multiplicity of lesions.

In the monkey the MLF is about 1 mm. in diameter; so it is difficult to destroy only one MLF. The best we could do was to cut the medial aspect of the MLF on each side of the midline. This resulted in the syndrome in which there was weakness of adduction of the eyes on the two sides, nystagmus in the adducted eye on each side, and, of significance in the light of more recent experiments, nystagmus on upward gaze, with partial ptosis. I am emphasizing this point because we have some information that as soon as both sides of the brain stem are implicated across the median raphe, the vertical components of the eye movements are disturbed. In these monkeys there were defects in upward gaze, manifested by a nystagmus.

Pathological Studies of Infratentorial Vascular Malformations. DR. STANLEY M. ARONSON, DR. HARRY A. KAPLAN, and DR. HARUO OKAZAKI, Brooklyn.

Pathological studies were performed in 20 cases of vascular malformation within the infratentorial neural tissues. The initial lesion of the ultimate racemose mass would appear to be a residual, direct shunt between artery and vein, a perpetuation of a state transiently normal during embryonal development. As a result of the transmission of pulsating arterial pressure into venous channels, a responsive phlebosclerosis, dilatation, mineralization, and arterialization develop. Veins which usually would become vestigial may be kept patent by these heightened tensions, thus increasing the number of veins in the malformation.

Postmortem venography shows that much of the cerebellar venous drainage empties into the vein of Galen. The venous malformations of this region tend to occur in these areas of collecting veins. The arterial contribution is generally traced to the circumferential branch of the superior cerebellar artery. The sagittal malformations, in this series, are the largest and tend to hemorrhage. Those within the deep white matter are often of little clinical import.

Since these malformations are the end-result of increased and sustained pressures exerted through an otherwise normal venous drainage system, they represent passively dilated, rather than heterotopic, veins. Their distribution, therefore, corresponds to the normal venous ramifications of the area involved.

Discussion

DR. E. JEFFERSON BROWDER, Brooklyn: First, I want to thank Dr. Aronson for reviewing with me the material which is the basis of his presentation. It is to be emphasized that vascular malformations of the type being considered comprise an arterial feeder, a vascular pool, and numerous dilated veins. The dilated veins make up the obvious mass; however, the arterial feeder is the important vascular channel so far as the surgeon is concerned. Occlusion of this feeding artery and obliteration of the arteriovenous pool is the logical therapeutic procedure in patients whose physical status permits operative approach to their problem. It is not necessary to extirpate the large venous channels.

Neurological Concomitants of the Tranquilizer Therapies. DR. SIDNEY MERLIS.

The newer drugs used in the treatment of psychiatric disorders have significant neurological side-effects, varying from rather mild to severe in character. The neurological syndromes seen can be listed as follows: convulsive seizures, Parkinsonian-like syndrome, blurring of vision, myoclonic twitchings, autonomic nervous disturbances, tonic-torsion spasms of the neck, dysphagia, spastic contractions of the jaw muscles, meningoencephalitis and a poliomyelitis-like disorder. The diagnosis of these syndromes depends upon eliciting the information that the patients have been receiving the tranquilizer drugs, and the treatment consists of specific therapy for the syndrome involved, i. e., anticonvulsive or anti-Parkinsonism therapy and the discontinuation of tranquilizer medication therapy. The incidence of these side-effects varies with the type of drug used but can appear in 10% to 20% of the patients receiving therapy.

Discussion

DR. S. BERNARD WORTIS: Dr. Merlis deserves our congratulations on an excellent paper on the neurologic complications of the newer tranquilizers.

One out of every three prescriptions in the United States today is for tranquilizer drugs. Seizures certainly are seen occasionally with the phenathiazines, especially in patients who have had convulsions before. Parkinson's syndrome is one of the common complications. We have seen most of these complications with prochlorperazine (Compazine) and trifluoperazine (Stelazine).

We should remember that there are some other neurological effects, in addition to the extrapyramidal syndrome and convulsive seizures. One sees dystonic syndromes, spasms of the neck, tongue, and pharynx muscles, hyperthermia, hypothermia, a myasthenia-gravis-like picture, a bulbar-palsy-like syndrome, pseudotabes, acute choreoathetosis, and cerebellar signs. The effects on the autonomic nervous system include hypotensive crises, activation of peptic ulcer, tachycardia, nasal congestion, excessive salivation, vomiting, etc. The toxic and allergic manifestations occasionally seen include jaundice, agranulocytosis, purpura, and dermatitis.

At the present time, although the newer drugs have been most useful in selective cases, we have no evidence that they do anything but relieve certain manifestations of psychosis; none of them seems to alter the basic disorder.

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Regular Meeting, Feb. 7, 1958

Controlled Pneumoencephalography with Small Amounts of Air in Diagnosis of Acoustic Tumors. DR. FREDERICK MURTAGH, DR. MICHAEL SCOTT, and DR. H. M. STAUFFER (by invitation).

The principles of controlled pneumoencephalography and the positive-pressure technique of air injections have been clearly outlined and used by Robertson and Lindgren. The method has been emphasized by Shapiro in this country. Ten to fifteen cubic centimeters of air injected into the spinal subarachnoid space without the prior removal of spinal fluid will raise the pressure slightly but will not disturb the subarachnoid cisterns or produce a shift of the intracranial structures, which is

highly dangerous in the presence of an expanding lesion. The method is particularly valuable in the visualization of the cerebellopontile cisterns as a method of ruling out a cerebellopontile tumor. The patient is placed in a sitting position in front of a Potter-Bucky holder with the head angulated forward 40 degrees with the horizontal beam of the x-ray tube. Fifteen cubic centimeters of air is injected, and the x-ray film is exposed at the end of the injection. This will visualize the cerebellopontile cisterns and demonstrate the presence or absence of a tumor in this region. The procedure is contraindicated in the presence of marked increased intracranial pressure, as indicated by papilledema.

Discussion

DR. MATTHEW T. MOORE: I would like to inquire of Dr. Murtagh how many false-positive and false-negative results he has had with this test.

DR. ROBERT A. GROFF: Dr. Murtagh is to be complimented on this ingenious idea. Partial pneumoencephalography has been used by others, as well as in cases of increased intracranial pressure. When it is done in the latter instance, I feel that, as a precautionary measure, burr holes should be placed in position for tapping of the ventricles, so that if an unfortunate reaction occurs it can be used as an emergency measure. If it is possible to visualize the cisternae in the vicinity of the cerebellopontile angle consistently, this test is very valuable. It would appear to me that it has not been used in sufficient cases to permit one to determine the practicality of the test. This brings up the question of whether the author had any false-positive results. It would seem to me that Dr. Murtagh's idea has merit and, therefore, deserves further investigation.

DR. HENRY A. SHENKIN: We have used a fractional technique in the diagnosis of chiasmal lesions with great success in the past year and can particularly confirm the report that this method seldom produces any reaction in the patient.

DR. AXEL OLSEN: There are two suspected acoustic neuroma cases currently at Philadelphia General Hospital, and we plan on using this test in them.

DR. MICHAEL SCOTT: What impresses me most about this test is the minimal reaction and the fact that an anesthetic is usually unnecessary. Partial encephalography is also helpful in diagnosing lesions in the supratentorial area. I would not recommend this technique in cases with increased intracranial pressure. This procedure may also be of value in visualizing arachnoidal adhesions or obliteration of the cisterna pontis following subarachnoid bleeding or meningitis, particularly if the patient has impaired hearing as a deficit.

Tic Douloureux: Treatment by the Combined Use of Hydrochloric Acid Therapy and Histamine Desensitization. DR. WILLIAM J. HANES, Wayne, Pa. (by invitation).

A new medical concept of the treatment of tic douloureux is presented, based on an allergic approach, employing HCl therapy orally, histamine desensitization, and antihistamine medication. Thirteen cases of tic douloureux and one case of herpes zoster involving the trigeminal nerve are reported. Complete histories, physical examinations, blood counts, and urinalyses were performed in each case. Because of a previous interest in the therapeutic results derived from HCl orally, gastric analyses were performed in each case. This study revealed in most cases an absence of free HCl or a decreased content of acid and served as the basis for the reasoning that this therapy was indicated. A theory as to the pathogenesis of trigeminal neuralgia, substantiated by therapeutic results, is proposed, and a practical and simple therapeutic procedure is outlined. Previous effective relief of this agonizing pain has been accomplished only by destroying the ganglion and the sensory nerves surgically, chemically and by boiling water. This method described herein makes these heroic procedures unnecessary. A follow-up of the cases presented for a period of six months to nine years is included. This rules out any likelihood of spontaneous remissions. Five of the patients had recurrences of their pain and were relieved again when the allergic therapeutic approach was used, this being further evidence to support the theory presented.

Discussion

DR. A. M. ORNSTEEN: This is an excellent presentation, with all of the facts stated clearly and fairly. It would be unfair to contradict some of Dr. Hanes' statements, because he has at times pointed out their contradictable nature. Who of us can voice serious objection without comparable experience; and again, who of us could take nine years to ascertain the value of any particular method. There is much variability in the clinical presentments of tic douloureux. The chief difficulty in this regard is the spontaneous remitting and recurring characteristics of the clinical course, which make it particularly difficult to evaluate a therapeutic method. I should say that Dr. Hanes' theoretical basis for his therapeutic method cannot be attacked in the face of his results presented in the protocol. Theoretical concepts on this subject vary widely. A basic question in a presentation of this sort is whether all the cases presented were of typical tic douloureux or true trigeminal neuralgia. This is merely a pragmatic statement, rather than doubtful reflection. Any form of therapy that affords relief to the patient is worthy of

serious consideration. For some time now, parenteral cyanocobalamin (vitamin B_{12}) therapy was popular, but latterly seems to be somewhat on the wane. Dr. Hanes is to be commended on his credibility of motivation in this case of clinical investigation.

DR. CHARLES RUPP: All neurologists are familiar with posterolateral sclerosis, which invariably is associated with achlorhydria. I have never seen a case of tic douloureux associated with posterolateral sclerosis. I have not been too sure that the cases presented are those of tic douloureux. In one case the pain came on when the patient was only 9 years of age, and a number of the other patients had the onset very early in life. In my experience, tic douloureux usually occurs in patients in the middle and late years of life. I would like to know how many of the patients presented have been seen by a competent neurologist who corroborated the diagnosis.

DR. SAMUEL B. HADDEN: This bit of clinical research is rather significant to me, if for no other reason than the fact that it was not supported by a grant from the United States Public Health Service or some foundation or pharmaceutical company. It was carried out by Dr. Hanes in the course of his practice, with his own patients, and individually financed. Dr. Hanes has presented his procedure, the rationale of it, and his evaluation of the results. There may be a question of the diagnosis in some of his cases, but there can be little doubt that improvement occurred. Others might not be able to duplicate the results, but this would not imply that Dr. Hanes did not obtain the results claimed. It would simply demonstrate once more that the confidence and enthusiasm of a true physician who seeks relief for a suffering patient can many times be a most effective therapeutic agent in migraine, tic douloureux, and other such disorders, in which there may be a strong functional element.

DR. HENRY A. SHENKIN: We have all listened to various "cures" that have been advocated for major trigeminal neuralgia. These have not held up, and undoubtedly the original reports took advantage of the natural remission rate in this disease and included cases other than of true tic douloureux. The present report is based upon a very vague theory, and the treatment is prolonged, so that one may wonder whether the ultimate results will be any different from those of numerous treatments previously suggested so enthusiastically by their proponents.

DR. HARVEY BARTLE JR.: I have followed Dr. Hanes' work for several years and have had the privilege of seeing one of his patients. He has shown great perseverance in this study, for which he should be commended. I hope that he may be able to continue this work and report to us again at a later date.

DR. WILLIAM J. HANES, Wayne, Pa.: I appreciate both your compliments and your criticisms. I do not claim that this method of treatment is a permanent cure; rather, I present it as a means of allaying symptoms. If you could see the reactions of these patients who, after experiencing a recurrence of their pain, are relieved within two or three minutes by the use of intravenous diphenhydramine (Benadryl), I feel sure that you would be impressed. In nine years I have treated 14 patients with tic douloureux, each patient having been referred by a patient previously relieved of this agonizing pain. In answer to Dr. Shenkin: Most of the patients reported on this evening had been seen by neurologists prior to coming to me, one man having been seen by four neurologists, two of whom are present tonight. Finally, after many alcohol injections and a supraorbital avulsion, which failed to give relief, he was referred to me and responded to the described treatment. Dr. Bayard Horton, of the Mayo Clinic, feels that I have found the solution to this problem from an approach based on disturbed chemistry and physiology. It was Dr. Horton's opinion that if the method of this treatment is worth while, it will last; if not, it will die, as it should.

Sensitivity to Poliomyelitis Vaccine: Report of a Case. DR. MARJORIE A. MEYER (by invitation), DR. RICHARD A. BRUNNER (by invitation), and DR. SAMUEL B. HADDEN.

A 28-year-old married woman complained of generalized weakness and progressive ascending paralysis two hours after receiving her second poliomyelitis vaccination, which followed the first by one month. The paralysis manifested itself by numbness and tingling in the fingers and the toes at the onset, and then generalized weakness, becoming progressively worse, so that the patient was unable to walk and finally could not even turn the pages of a book and had difficulty in breathing. The spinal fluid showed no cells; the spinal fluid culture was negative; total protein was 67 mg. %. Blood and stool specimens were all negative for poliomyelitis virus. X-rays of the chest, the entire spinal column, and the skull were all negative for malignancy. The remainder of her laboratory studies were all within normal limits. Six months prior to the present illness, the patient had a radical mastectomy and a hysterectomy. Eighteen months prior to admission she had had severe mumps and "viral" gastroenteritis. During her hospitalization for her operations, and on several other occasions, she had received penicillin, without any untoward reactions, and had no past history of allergy. The patient was treated with corticotropin. The duration of illness was six weeks, with complete recovery in two months.

Discussion

DR. ANTHONY S. TORNAY: The following experiences have occurred at the Philadelphia Municipal Hospital concerning poliomyelitis vaccine administration and its sequelae. The 4-year-old daughter of a physician was given the vaccine as suggested by the manufacturer, using the first batch of vaccine released; it was not the Cutter vaccine. The child developed severe meningitis and a secondary encephalitis. She developed numerous complications and died within 48 hours after admission. The Virus Laboratory reported Type 1 poliomyelitis virus. The second child admitted was an 8-year-old girl who developed complete paralysis of the left arm following the injection of vaccine in this arm. There was an elevation of the spinal fluid cell count, and the diagnosis of poliomyelitis was established. Rapid recovery occurred in three weeks. The third child was a boy who was admitted with bilateral weakness through the shoulder girdles. He also had received the vaccine. There was an elevation of the spinal fluid cell count. He recovered rapidly. It is to be noted that the last two patients received the modified vaccine, which was supposed to be produced under a more rigid control.

DR. CHARLES RUPP: Dr. Meyer has presented fairly convincing evidence for an allergic reaction to the vaccine, but I wonder whether she and her co-author have considered the possibility that the patient may have had a mild attack of paralytic poliomyelitis.

DR. SAMUEL B. HADDEN: Dr. Meyer reported this case to you at my request because it was one in which the patient developed widespread evidence of anterior-horn-cell involvement after the second injection of poliomyelitis vaccine. It is our belief that the lower motor neuron cells were sensitized by the first injection, and that when the second was given there was an intracellular response which resembled acute poliomyelitis and which, for a time, presented threatening manifestations. On admission there was widespread loss of power, absence of tendon reflexes and diminished muscle tone. No sensory changes were ever present. Eventually muscle wasting became apparent, and there were pathological electrical responses. We have not considered this occurrence an actual poliomyelitis infection because there was no elevation of temperature. Onset was sudden, and evidence of widespread involvement developed rapidly. No active virus was found in the spinal fluid. The reaction did not resemble an anaphylactic response. This patient was never acutely ill. No meningeal involvement was noted. It is impossible to determine whether or not her mumps played any role, but we have discarded any thought of her breast cancer having any causal relationship. This case has been reported to call attention to the possibility of a cellular sensitivity developing during immunization against poliomyelitis.

News and Comment

ANNOUNCEMENTS

American Board of Psychiatry and Neurology, Inc.—The American Board of Psychiatry and Neurology, Inc., wishes to announce the following schedule of examinations:

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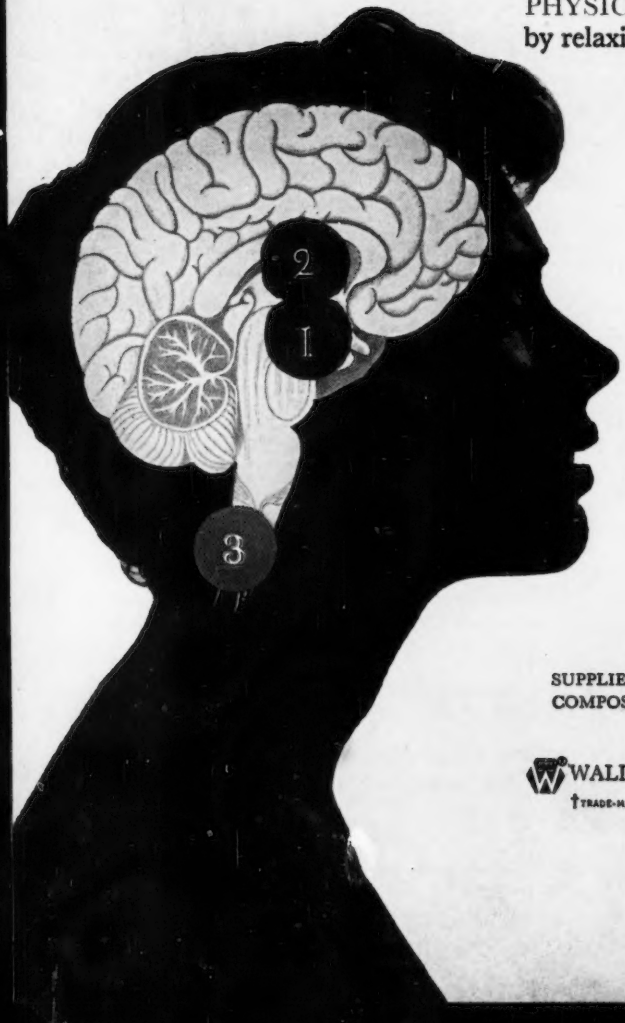

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Klimczynski, J.J.J.T.: Treatment of Chronically Ill Psychotic Patients with Trifluoperazine: A Preliminary Report, *ibid.*, pp. 101-112.

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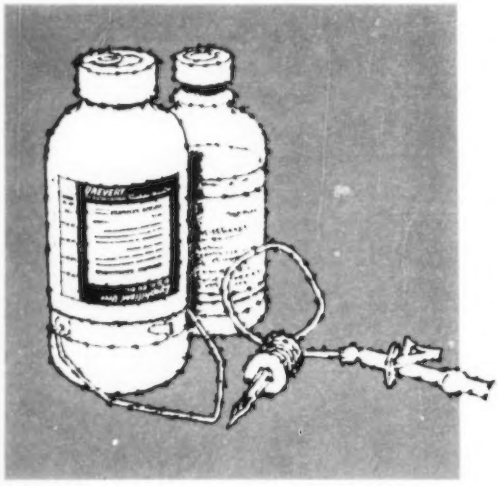

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†Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure. The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, August, 1958, p. 907.

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